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## BENIGN NEOPLASMS OF THE GALLBLADDER

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Benign neoplasms of the gallbladder occur so rarely that even in a large surgical practice one encounters few of them; for this reason all studies of these growths have been based on only a few cases. We wish to present a clinical and pathologic study of the benign tumors of the gallbladder encountered at operation at the Mayo Clinic from Jan. 1, 1906, to Dec. 31, 1938, inclusive. The group comprises 45 gallbladders containing one or more polypi, 103 containing adenomyoma and 2 containing fibroma. All the specimens except 3 were obtained by cholecystectomy; 3 were taken for biopsy—2 of the 3 at cholecystostomy and 1 at gastric resection for carcinoma of the stomach. Papilloma of the gallbladder, as has been pointed out by MacCarty,<sup>1</sup> by Phillips,<sup>2</sup> and by Graham, Cole, Copher and Moore,<sup>3</sup> is not a true neoplasm and hence was not included in this study.

### POLYPUS

*Literature.*—Like all benign neoplasms of the gallbladder, polypus of the gallbladder is rare. No reliable figures concerning its incidence are available. Finkelstein<sup>4</sup> estimated that 0.5 per cent of all gallbladders

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Abridgment of a thesis submitted by Dr. Shepard to the faculty of the University of Minnesota Graduate School in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. MacCarty, W. C.: The Pathology of Gallbladder Disease, in Walters, W., and Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940, pp. 77-94.

2. Phillips, J. R.: Papilloma of the Gall Bladder, Am. J. Surg. **21**:38-42 (July) 1933.

3. Graham, E. A.; Cole, W. H.; Copher, G. H., and Moore, S.: Diseases of the Gall Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928, pp. 184-190.

4. Finkelstein, cited by Pytel.<sup>15</sup>

removed by operation contain a benign tumor. Polypi may occur singly or as multiple tumors. In a few cases the entire mucosa is involved (polyposis).

Causation: Doljanski and Roulet<sup>5</sup> expressed the belief that benign neoplasms of the gallbladder arise as growths of connective tissue under the influence of the covering epithelium, just as specific types of connective tissue are differentiated from undifferentiated connective tissue in the fetus under the influence of the epithelium of the organ in question.

Klose and Wachsmuth<sup>6</sup> stated that the polypus originates by growth of the glands of the gallbladder and subsequent hyperplasia of the connective tissue stroma.

Virchow<sup>7</sup> expressed the belief that the growth of all fibroepitheliomas of the gallbladder is due to growth of connective tissue and that the epithelium merely increases to fulfil its normal function as a covering for tissue.

Birch-Hirschfeld,<sup>8</sup> Eberth,<sup>9</sup> Hanau<sup>10</sup> and Pfannenstiel<sup>11</sup> said that the impulse to the growth of a tumor of the gallbladder comes from the epithelium and is a response to a general urge to epithelial growth.

Abell,<sup>12</sup> Klose and Wachsmuth, Kovács,<sup>13</sup> Mölle,<sup>14</sup> Phillips and Pytel<sup>15</sup> all stressed the role of chronic infection and inflammation and the trauma of stones as the inciting stimulus to the formation of a tumor.

Pathologic Description: From the first description of a papilloma of the gallbladder by Heschel<sup>16</sup> in 1852, the nomenclature of the fibro-

5. Doljanski, L., and Roulet, F.: Ueber gestaltende Wechselwirkung zwischen dem Epithel und dem Mesenchym, zugleich ein Beitrag zur Histogenese der sogenannten "Gallengangswucherungen," Virchow's Arch. f. path. Anat. **292**:256-267, 1934.

6. Klose, and Wachsmuth, W.: Seltene chirurgische Erkrankungen des Gallensystems, Arch. f. klin. Chir. **123**:1-6, 1923.

7. Virchow, R.: Die krankhaften Geschwülste, Berlin, August Hirschwald, 1864-1865, vol. 2, pp. 170-384.

8. Birch-Hirschfeld, F. V., cited by Konjetzny, G. E.: Pathologische Anatomie und Physiologie der Gallenblasen- und Gallengangserkrankungen, Ergebn. d. allg. Path. u. path. Anat. **14**:792-821, 1910.

9. Eberth, cited by Schoenlank.<sup>17</sup>

10. Hanau, cited by Schoenlank.<sup>17</sup>

11. Pfannenstiel, cited by Schoenlank.<sup>17</sup>

12. Abell, I.: Papilloma and Adenoma of Gall-Bladder, Ann. Surg. **77**:276-280 (March) 1923.

13. Kovács, A.: Cholecystitis Polyposa (Fibroepithelioma Hieronymi) des Hundes, Zentralbl. f. allg. Path. u. path. Anat. **56**:377-380 (Feb. 10) 1933.

14. Mölle, H.: Ueber Papillome der Gallenblase, nebst Mitteilung eines selbst beobachteten Falles, Beitr. z. klin. Chir. **99**:173-185, 1916.

15. Pytel, A.: Zur Kasuistik der benignen Geschwülste der Gallenblase, Zentralbl. f. Chir. **57**:2240-2242 (Sept 6) 1930.

16. Heschel, R., cited by Schoenlank.<sup>17</sup>

epithelial tumors of the gallbladder has been confused by the use of a multiplicity of terms to describe the same type of tumor and further by the use of the same term to describe different types of tumor. Polypus of the gallbladder has been termed polypus, cholecystitis polyposa, fibroepithelioma and papilloma; most of the last named are true papillomas, but at least a few of the so-called large papillomas are polypi by description, and Phillips and Schoenlank<sup>17</sup> distinguished them as such.

Kovács, Ringel<sup>18</sup> and Schoenlank described the polypus in its simplest terms as a framework of vascular connective tissue covered by high columnar epithelium with basal nuclei and the presence of an occasional goblet cell. The tumor is sessile or pedunculated and uniformly small, rarely exceeding 8 mm. in diameter. Predilection for any particular portion of the gallbladder is not observed. Fine capillary networks are seen throughout the stroma. Large, clear cells containing doubly refractile neutral fat are often present in large numbers in the framework of connective tissue. Inflammatory cells, especially lymphocytes, are the rule rather than the exception.

Kovács and Klose and Wachsmuth described polyposis, or a general involvement of the mucosa by polypi; the pathologic characteristics of the constituent growths are identical with those of the single tumor.

Unlike polypi of the stomach and the colon, polypus of the gallbladder rarely if ever becomes malignant; no instance of malignant change of a polypus of the gallbladder has been reported in the literature with convincing proof. In some cases, such as the now famous case reported by Pels-Leusden,<sup>19</sup> malignant change has been reported, but it has been found later that the change was benign.

**Clinical Picture:** It has been pointed out repeatedly that the response of the gallbladder to any change, whether inflammation, trauma or tumor, is necessarily limited, owing to the simple structure of the gallbladder. No definite or characteristic symptoms have been described for polypus of the gallbladder, and the clinical picture presented has been attributed to the accompanying cholecystitis or cholelithiasis or both.

**Diagnosis:** For lack of a characteristic picture, polypus of the gallbladder has been diagnosed preoperatively only by roentgenography.

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17. Schoenlank, A.: Ueber das Papillom der Gallenblase, Frankfurt. Ztschr. f. Path. **16**:293-315, 1915.

18. Ringel: Ueber Papillom der Gallenblase, Centralbl. f. Chir. **26**:129-130 (April) 1899.

19. Pels-Leusden, F.: Papilläre Geschwülste der Gallenwege, Verhandl. d. deutsch. Gesellsch. f. Chir. **33**:85-89, 1904; Ueber papilläre Wucherungen in der Gallenblase und ihre Beziehungen zur Cholelithiasis und zum Carcinom, Arch. f. klin. Chir. **80**:128-160, 1906.



Kirklin <sup>20</sup> and, later, Moore <sup>21</sup> and Hefke <sup>22</sup> all described their roentgen diagnosis. Characteristics of the roentgen picture of polypus of the gallbladder are as follows:

1. There is a radiolucent defect in the shadow of the dye-filled gallbladder; this defect is more radiolucent than the most radiolucent non-opaque stone.
2. The defect is small and round, rarely more than 1 cm. in diameter.
3. The defect is usually single; if there are multiple defects, they are discrete.
4. The defect is marginal and is best seen in a tangential view which shows the defect continuous with the wall of the gallbladder.
5. The defect is best seen in the twenty-four hour film.
6. The shadow of the gallbladder is usually good, for the gallbladder concentrates the dye well; this has been shown by Caylor and Bollman <sup>23</sup> to be due to the concentrating powers of the hypertrophic rugae which usually accompany the growth.
7. No characteristic location of the defect has been noted.

Complications: Hromeda,<sup>24</sup> King and MacCallum<sup>25</sup> and Klose and Wachsmuth described prolapse of a pedunculated tumor causing obstruction at the neck of the gallbladder. Phillips and Risak<sup>26</sup> both saw polypi that had become detached and acted either as a stone or as the nidus for the formation of stone.

*Findings.*—In all there were 45 gallbladders, each of which contained one or more polypi. In roughly every 100 cases of cholecystectomy, the gallbladder contained one or more polypi. This, however, gives no inkling of the incidence in the general population. The sex distribution was about equal (53 per cent in women and 47 per cent in men). The

20. Kirklin, B. R.: Cholecystographic Diagnosis of Papillomas and Other Tumors of the Gallbladder, Proc. Staff Meet., Mayo Clin. 5:336-337 (Nov. 19) 1930.

21. Moore, C.: Cholecystographic Diagnosis of Papillomas and Tumors of Gallbladder, Am. J. Roentgenol. 33:630-635 (May) 1935.

22. Hefke, H. W.: Die Diagnose von Papillomen der Gallenblase mittels Cholezystographie, Röntgenpraxis 3:871-873 (Oct. 1) 1931.

23. Caylor, H. D., and Bollman, J. L.: The Bilirubin Content of Gallbladder Bile in Cholecystic Disease, Arch. Path. 3:993-1001 (June) 1927.

24. Hromeda, G.: Ein Fall von Myom der Gallenblase, Zentralbl. f. Chir. 60: 2254-2256 (Sept. 23) 1933.

25. King, E. S. J., and MacCallum, P.: Cholecystitis Glandularis Proliferans (Cystica), Brit. J. Surg. 19:310-323 (Oct.) 1931.

26. Risak, E.: Ueber polypöse Tumoren der Gallenblase, Beitr. z. klin. Chir. 138:382-390, 1926.

youngest patient was 34 years old; the oldest, 64 years, and the average age, 50.2 years.

**Gross Pathologic Characteristics:** In 28 per cent, the polypus was single; in 72 per cent, there were multiple tumors; in 2 cases of the latter type, the condition is best described as polyposis of the gallbladder. The polypi occurred in all parts of the viscus without predilection for any one location. All were pedunculated. They were small as a rule, averaging 3 mm. in diameter; the extremes varied from 1 to 8 mm. in diameter. In addition, the gallbladders frequently contained other pathologic growths as well as polypi: Cholesterosis (strawberry gallbladder) was seen in 37 per cent; adenomyoma occurred in 9 per cent, and gallstones were found in 68 per cent. These were divided equally between single and multiple stones; all varieties of stone occurred, more than one type being present in the same viscus fairly frequently.

**Microscopic Pathologic Characteristics:** The polypus is a fibro-epithelial tumor consisting of a stalk and a supporting stroma of white fibrous tissue containing a rich network of capillaries. The stroma is clad by a single layer of tall columnar epithelium with large, oval, dark-staining, basally placed nucleus and clear cytoplasm and resembles normal epithelium of the gallbladder in all respects. In the stroma is seen an occasional acinus with a small lumen lined by epithelium of the same character as that of the epithelium which covers the polypus. In the polypi examined, goblet cells were scarce, occurring in only 9 specimens. The multiple tumors and the lesions in the 2 cases of polyposis resembled the single growths in all respects. There were abundant signs of chronic inflammation throughout the wall of the gallbladder; however, they were no more striking in the polypus than in the uninvolved portions of the wall. Lymphocytes varying from scattered cells to solid sheets or clumps were present in every specimen; in 22 there was noticeable congestion, especially in the vessels of the fibrosa. Rokitansky-Aschoff sinuses occurred in 5 cases (11 per cent). In 20 instances (44 per cent), the polypus contained large light-staining cells with foamy cytoplasm (infiltration of cholesterol). In 29 (64 per cent), the mucosa was hyperplastic. As a rule, the muscularis was thickened, averaging 2 mm. (average thickness of normal muscularis, 0.5 mm.).

In 1 gallbladder, two polypi were present. No gross difference from the other polypi studied was apparent, but on microscopic examination regions of adenocarcinoma, grade 1 (Broders' method), were observed in both. There was loss of cell outline; an occasional mitotic figure was to be seen, and the nuclei were dark staining. Invasion of the regions contiguous to the malignant region was beginning, but the stalk was not invaded (fig. 1).

**Clinical Picture:** A history of cholecystic disease (gas, belching, flatulence, pyrosis, sour eructations, sensation of heaviness, intolerance

to roughage, fats and greases and attacks of abdominal pain) was elicited in 38 cases (84 per cent). In 24 (53 per cent) there was a history of colicky pain in the upper part of the abdomen, usually in the right upper quadrant and often extending through or around the trunk to the back; this pain was severe enough to waken the patient and required opiates for relief. In 9 cases (20 per cent), jaundice had been present at least once. The duration of symptoms varied from two weeks to thirty years; the average duration was seven and four-tenths years.

Examination revealed tenderness in the right upper quadrant of the abdomen in 20 cases (44 per cent); 3 patients were icteric.

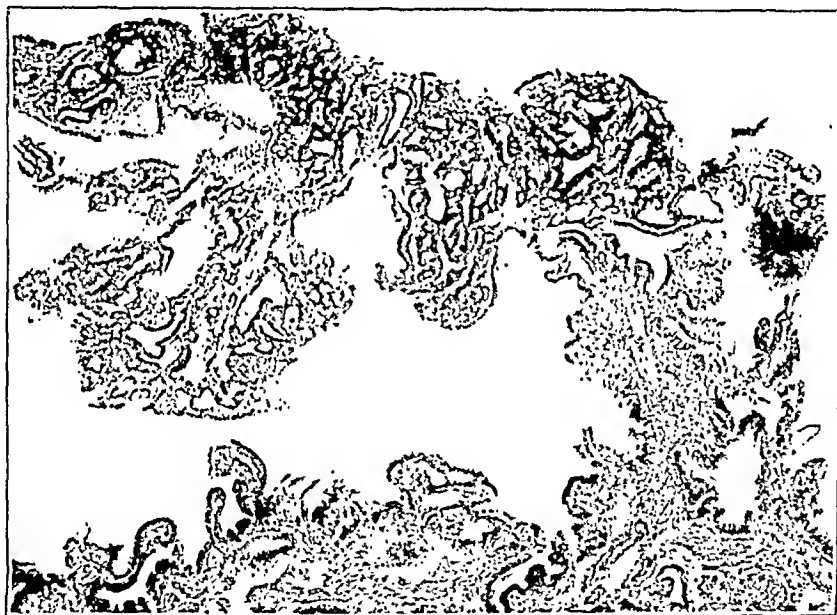


Fig. 1.—Polypus of the gallbladder (stained with hematoxylin and eosin;  $\times 25$ ). This polypus contained a region of adenocarcinoma (grade 1).

**Diagnosis:** A clinical diagnosis of cholecystic disease was made in 38 instances (84 per cent). In 2 cases, a preoperative diagnosis of tumor of the gallbladder was hazarded by virtue of cholecystography. Forty-one patients underwent cholecystography by the oral dye method. Of these, 33 (80 per cent) showed some abnormality—stones or poor or no concentration of the dye or both; 2 of these 33 exhibited a defect that was diagnosed correctly as tumor; in both instances there was no impairment of ability to concentrate the dye. Eight patients (20 per cent) showed normal function and no shadow defects of stone or tumor.

**Complications:** With the exception of the 1 viscus (two polypi) in which there was malignant change, there were no complications.

The incidence of polypus of the gallbladder in this series, roughly about once in every 100 gallbladders removed by operation, is in agreement with the findings of Chiray,<sup>27</sup> Klose and Wachsmuth, Kovács, Risak and Schoenlank.

No predilection for any one part of the gallbladder was revealed in this series nor is any mentioned in the literature.

It is significant that polypi do not occur in otherwise normal gallbladders; in every case there was some sign of chronic inflammation, and in 68 per cent, stones were present. From these findings it seems justifiable to assume that chronic inflammation and the trauma of stones play a role in the causation of polypus of the gallbladder, an opinion voiced by Klose and Wachsmuth, Kovács, Mölle, Pels-Leusden, Sand and Mayer<sup>28</sup> and Schoenlank.

There is no evidence to show whether the tumor started as a connective tissue growth, as both Schoenlank and Virchow stated, or as an epithelial growth, as held by Birch-Hirschfeld, Hanau, Eberth and Pfannenstiel.

Two of the gallbladders were so extensively involved that the condition is best classified as polyposis and may have been due, as polyposis of the colon is, to an inherent capacity for fibroepithelial growth.

In two polypi, both in the same gallbladder, definite adenocarcinoma, grade 1 (Broders' method), was present; they had the same stimulus (chronic inflammation and stones) as the other polypi in which there was no malignant change. Did trauma from the single stone in this gallbladder play a part in causing the malignant change? In 68 per cent of all the polypus-containing gallbladders there were one or more stones; yet in only two polypi (in the same gallbladder) was there a malignant change. Practically all authors who have written about malignant lesions of the gallbladder have stressed the possible role of gallstones in the causation of these lesions.

Most authors agree that benign tumors of the gallbladder do not present any characteristic clinical picture and that, except for roentgenography, they are not suspected preoperatively; the usual syndrome is that of the concomitant cholecystitis or cholelithiasis or both. The findings in this series of cases are in agreement with this opinion; in only 2 cases was tumor suspected preoperatively, and in these the suspicion was by virtue of defects in the shadows of the roentgenograms of normally functioning gallbladders.

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27. Chiray, M., and Pavel, I.: *La vésicule biliaire: Anatomie, physiologie, sémiologie, pathologie, thérapeutique*, Paris, Masson & Cie, 1927, pp. 491-502.

28. Sand, R., and Mayer, L.: *Transformation de la vésicule biliaire tout entière en un kyste papillifère*, Arch. de méd. expér. et d'anat. path. **23**:523-528, 1911.

## ADENOMYOMA

*Literature.*—This tumor has been described as adenoma by Buzzi and Lascano Gonzalez,<sup>29</sup> Király,<sup>30</sup> Robson<sup>31</sup> and Wellbroch,<sup>32</sup> as myoma by Hromeda, as cholecystitis glandularis proliferans by King and MacCallum, as cystadenoma by Kordenat<sup>33</sup> and by Shambaugh,<sup>34</sup> as fibromyoadenoma by Weidlinger,<sup>35</sup> as cholecystitis cystica by Bodnár<sup>36</sup> and as adenomyoma by Eiserth<sup>37</sup> and by Nicod.<sup>38</sup> All the terms except adenomyoma have the disadvantage of being used to describe other tumors in addition to the tumor under discussion. Adenomyoma seems the best designation for three reasons: first, it describes the constituent tissues of the tumor; second, it has not been used for other tumors or inflammatory changes, and, lastly, this tumor is analogous to adenomyoma of the uterus.

*Incidence:* This also is a rare tumor. Eiserth found 13 cases in a "little less than 4,000 autopsies." King and MacCallum found it in 9.5 per cent of 400 gallbladders removed for cholecystitis or cholelithiasis. Aschoff and Bacmeister<sup>39</sup> found it in 3 per cent of the patients studied for cholecystitis or cholelithiasis or both. Lubarsch<sup>40</sup> found this tumor in 5 per cent of necropsies, and Nicod found it in 1 per cent. Nicod was the only author who studied its sex distribution, and he found it equally distributed. He also found it "at almost all ages." However, both Luschka<sup>41</sup> and Eiserth emphasized that it is rarely if ever seen in the newborn or in children and is encountered most frequently in patients in their fifties.

29. Buzzi, A., and Lascano Gonzalez, J. M.: Cholécytite chronique avec adénome, *Ann. d'anat. path.* **7**:943-948 (Nov.) 1930.

30. Király, J.: Gallenblasenadenom, *Arch. f. klin. Chir.* **178**:780-785, 1934.

31. Robson, A. W. M.: Adenoma of the Gall-Bladder, *Med.-Chir. Tr.*, London **88**:229-231, 1905.

32. Wellbroch, W. L. A.: Adenoma of the Gall Bladder, *Am. J. Surg.* **23**:358-360 (Feb.) 1934.

33. Kordenat, R. A.: Cystadenoma of the Gallbladder: Report of Case, *Wisconsin M. J.* **29**:634-637 (Nov.) 1930.

34. Shambaugh, P.: Multilocular Papillary Cystadenoma of the Gall Bladder, *Am. J. Surg.* **22**:229-231 (Nov.) 1933.

35. Weidlinger, E.: Fibromyoadenom des Gallenblasenfundus, *Arch. f. klin. Chir.* **153**:180-182, 1928.

36. Bodnár, L.: Cholecystitis cystica, *Virchows Arch. f. path. Anat.* **238**:359-365, 1922.

37. Eiserth, P.: Adenomyome der Gallenblase, *Virchows Arch. f. path. Anat.* **302**:717-723, 1938.

38. Nicod, J.: L'adénomyome du fond de la vésicule biliaire, *Ann. d'anat. path.* **4**:133-139 (Feb.) 1927.

39. Aschoff, L., and Bacmeister, A.: Die Cholelithiasis, Vienna, Gustav Fischer, 1909, p. 117.

40. Lubarsch, O., cited by Eiserth.<sup>37</sup>

Causation: There is lack of agreement as to the causation of these growths, although most writers have stated that they are either of congenital origin or due to inflammation and infection in the gallbladder.

(a) Congenital Origin: Aschoff and Bacmeister found little or no inflammation in some of their cases of adenomyoma and therefore said that adenomyoma is not due to inflammation. They expressed the belief that the tumor is a congenital anomaly analogous to the misformations of tissue in the tip of Meckel's diverticulum. Abell, Kordenat and Ribbert<sup>42</sup> all referred to Cohnheim's<sup>43</sup> hypothesis of displacement of embryonic cells during fetal development and the subsequent growth of these cells to form a tumor. However, neither Abell nor Kordenat expressed the belief that this is the source of these tumors. Buzzi and Lascano Gonzalez mentioned heterotopic epithelium and congenital malformation as well as inflammation and trauma of stones as causes of adenomyoma of the gallbladder. Eiserth expressed the belief that the tumor is hamartoblastoma and found other benign tumors elsewhere in the body in his necropsy material. He expressed the belief that the inflammatory changes are no greater than those in any chronically inflamed gallbladder; he concluded that the growth may be the result of "congenital but inactive proliferative anlage" which is stimulated by inflammation to grow, thus forming adenomyoma. Hromeda said that the tumor is an embryonal rest. Nicod expressed the opinion that it results from heterotopic epithelium or is of embryonic origin; however, he pointed out that the epithelium of the tumor is epithelium of the gallbladder and not from other parts of the gastrointestinal tract; in his opinion, the inflammation is secondary. Reimann<sup>44</sup> pointed out that a completely differentiated cell is incapable of mitosis and that "spare parts" (undifferentiated cells) must be present whenever regeneration, replacement, hyperplasia or repair is manifested. Thus the "multiple potency of cells" can explain the causation of this tumor without the necessity of Cohnheim's hypothesis.

(b) Inflammation, Infection and Trauma of Stones: Lubarsch expressed the belief that inflammation and infection stimulate heterotopic

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41. Luschka, H., cited by Halpert, B.: *Morphological Studies on the Gall-Bladder: I. A Note on the Development and the Microscopic Structure of the Normal Human Gall-Bladder*, *Bull. Johns Hopkins Hosp.* **40**:390-408, 1927; II. The "True Luschka Ducts" and the "Rokitansky-Aschoff Sinuses" of the Human Gall-Bladder, *ibid.* **41**:77-103, 1927.

42. Ribbert, cited by Kordenat.<sup>33</sup>

43. Cohnheim, J.: *The Pathology of Nutrition*, in *Lectures on General Pathology*, translated by A. B. McKee, London, The New Sydenham Society, 1889, vol. 2, pp. 746-821.

44. Reimann, S. P.: *Biology of the Cancer Cell*, in a *Symposium on Cancer*, Madison, University of Wisconsin Press, 1938, pp. 114-134.

epithelium of the gallbladder to grow and form adenomyoma; in his opinion, adenomyoma is not a disturbance of embryonic development; he did not find epithelial heterotopia without inflammatory changes. He was unable to find adenomyoma in the fetus or the newborn, and the average age of his patients was 53.4 years; all this speaks against a disturbance of embryonal development. Bodnár, by means of serial sections, showed that the epithelium of adenomyoma comes from the mucosa of the gallbladder. King and MacCallum expressed the belief that adenomyoma is formed by metaplasia (heteromorphosis) of the mucosa of the gallbladder; according to these authors, the tissue dedifferentiates because of the suitable stimulus, inflammation, and then redifferentiates to any type of epithelium in the gastrointestinal tract.

**Gross Pathologic Description:** This tumor is described as being invariably in the fundus of the gallbladder and as being single as a rule. Occasionally, the adenomyomatous tissue involves the entire gallbladder, turning it into a thick-walled inelastic sac. Its color has been described as varying from reddish brown to white. A more or less characteristic dimple is observed in the mucosa covering the convexity of the tumor. On cross section the center is often solid with small cavities at the periphery; these cavities may be so small that they are barely visible or may reach such a size that they are called cystadenoma. In general the cross section has a honeycombed appearance.

**Microscopic Pathologic Description:** The tumor may involve any or all parts of the wall of the gallbladder from the mucosa to the serosa. The tumor usually is described as consisting of glandular structures, tubules that resemble Rokitansky-Aschoff sinuses and cysts that are in reality dilated tubules, both lined by a single layer of tall columnar epithelium with clear cytoplasm and large, oval, basally situated nuclei. Mitosis, when present, is orderly, and there is no violation of contiguous tissue. All these glandular structures penetrate the muscularis and may reach as far as the subserosa. The tubules and the cysts are surrounded by irregular masses of felted smooth muscle. In places, especially about the larger cysts, the smooth muscle is arranged concentrically about the glandular tissue; Eiserth expressed the belief that this and the increase of elastic fibers about the cysts are phenomena of compression. Eiserth and Nicod are the only investigators who mentioned hyperplasia of the smooth muscle in the tumor. In serial sections, the connection of the glandular elements with the lumen of the gallbladder can be traced, but in a single section the glandular elements may appear to be isolated deep in the muscularis or the fibrosa; such sections have been diagnosed as "adenoma deep in the wall of the gallbladder," adenocarcinoma or pre-malignant lesion.

Buzzi and Lascano Gonzalez, Eiserth, Judd and Hoerner,<sup>45</sup> Király and Pytel all stated that a small number of these tumors become malignant, but of these authors, Eiserth alone presented a case of adenocarcinoma arising in an adenomyoma. Chiary, Nicod and King and MacCallum unequivocally stated that these tumors do not become malignant.

**Clinical Picture:** These tumors are silent because of their position and small size; the signs and symptoms present in such cases are due to the concomitant chronic inflammation or stones or both.

**Diagnosis:** To date a preoperative diagnosis is possible only by roentgenography. In the functioning or partially functioning gallbladder, an adenomyoma appears as a defect with the following characteristics: 1. The defect is more radiolucent than the most radiolucent stones. 2. It is small (always less than 2 cm.). 3. It is always single and is located in the fundus. 4. It does not change position when the patient is moved. 5. A tangential view at times shows the defect continuous with the wall of the viscus. 6. The defect is seen best in the twenty-four hour film.

**Complications:** Eiserth, King and MacCallum and Schoenlank described infection in the tumor with the formation of intramural abscesses which may rupture into the peritoneal cavity and cause peritonitis. Concretions in the component cysts may form intramural gallstones. Hromeda and King and MacCallum mentioned prolapse of the tumor causing obstruction of the cystic duct. Occasionally, a portion of the tumor may break off and serve as the nidus for the formation of stone, as described by Risak. The more hyperplastic portions of some tumors may be mistaken for adenocarcinoma, and, finally, as Eiserth has shown, adenocarcinoma may develop in an adenomyoma.

**Findings.**—The incidence of adenomyoma was the same as that of polypus—roughly 1 in every 100 cases in which cholecystectomy was performed. Adenomyoma occurred preponderantly among women—77 (75 per cent) as against 26 men (25 per cent). The average age of the patients was 48.9 years; the oldest patient was 70 years old and the youngest 22 years.

**Gross Pathologic Characteristics:** In 96 cases (93 per cent), the tumor was single and was located in the fundus of the gallbladder; in 5 cases there was generalized involvement (adenomyomatosis); in 1 instance, the tumor was in the body of the gallbladder, and in 1, it occurred near the cystic duct. In some specimens the tumor could be made out from the serosal surface as a roughly round whitish thickening of the wall. From the mucosal side, the tumor generally appeared as a circumscribed hemispherical thickening of the wall and usually pro-

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45. Judd, E. S., and Hoerner, M. T.: Adenoma and Adenomyoma of the Gallbladder, *S. Clin. North America* 15:1091-1097 (Oct.) 1935.



jected slightly into the lumen of the gallbladder; in no case was the growth pedunculated or sessile. About a third of the tumors (35 per cent) were less than 1 cm. in diameter; another third (34 per cent) were 1 cm. in diameter; only 5 tumors were 2 cm. or more in diameter. The tumors varied from yellowish white to gray red. As a rule, the edges of the growth were demarcated clearly from the adjacent wall of the viscus, but in a few instances the tumor blended with the wall so that it was difficult to distinguish the extent of the tumor until it was cross sectioned. In cut section, multiple small cystic regions gave the tumor a honeycombed appearance. Gallstones were present in 60 per cent of the specimens; stones of all types occurred, no variety predominating.

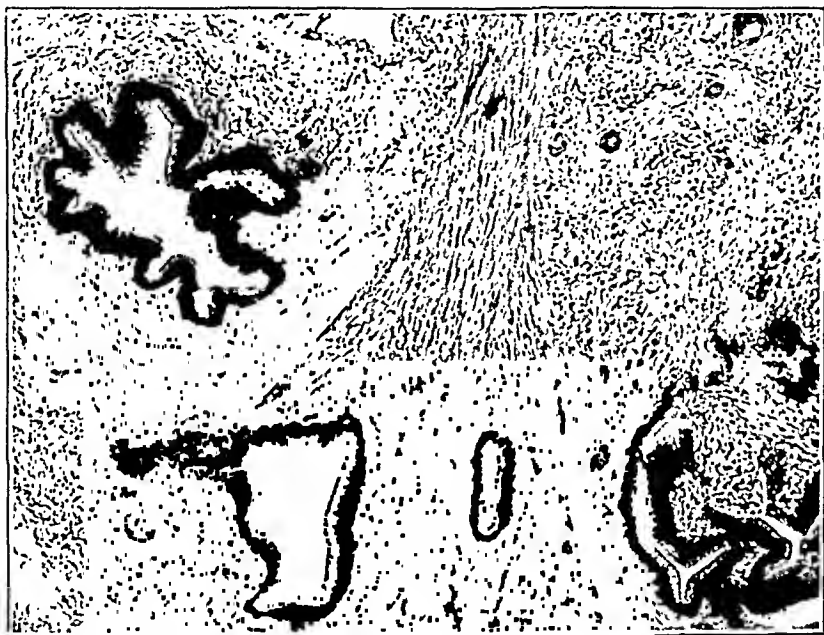


Fig. 2.—Adenomyoma of the gallbladder (stained with hematoxylin and eosin;  $\times 80$ ). The cysts contained invaginations of tall columnar epithelium supported by stroma of fibrous connective tissue. Note the bands of smooth muscle between cysts.

Intramural gallstones were present in 3 of the neoplasms. Cholesterosis (strawberry gallbladder) was present in 27 cases; papilloma was present in 12 and polypi in 4 cases.

**Microscopic Pathologic Characteristics:** The tumors consisted of epithelial-lined spaces surrounded by smooth muscle (fig. 2). The epithelium was a single layer of tall columnar cells made up of clear cytoplasm and large, oval, dark-staining, basally situated nucleus; it resembled the epithelium of the gallbladder in all respects. The epithelial-lined spaces varied from less than 1 mm. to 15 mm. in diameter. In places, the lining was regular and smooth; in others, it was thrown into small

folds formed by epithelial invaginations, giving the cyst a crenated appearance. Other cysts contained larger invaginations consisting of epithelium alone or epithelium on a stromal core of white fibrous tissue containing small blood vessels and an occasional strand of smooth muscle. At times the cysts anastomosed, but as a rule they were discrete.

In portions of 6 tumors, the epithelial elements were hyperplastic, forming a complex structure of small, adjacent, discrete and anastomosing cysts lined by tall columnar epithelium; in these hyperplastic regions there was no fibrous tissue or muscle. In none of these regions were there any signs of malignancy, and the regions changed over rather abruptly to the commoner picture already described. Smooth muscle surrounded the epithelial structures except in those regions just described; the muscle varied from irregular clumps of felted muscle to regular bands of smooth muscle. In some portions, the cysts were surrounded by loose white fibrous tissue, which separated them from the enveloping smooth muscle. The cystic structures could be seen to originate as downgrowths from the mucosa of the gallbladder when the section was cut at the right point. The muscularis of the tumor was hyperplastic; its average thickness in the tumor was 5.5 mm. (eleven times the thickness of the muscularis of the normal gallbladder). Although the muscularis of the uninvolved portions of the viscus often was thickened, it never approached the thickness of the adenomyomatous portion.

Signs of chronic inflammation were present in almost every case. Lymphocytes were present in more than normal number in almost every instance; they varied from scattered cells to sheets and clumps of lymphocytes. This might have been due to the presence of stones. Unlike polypi of the gallbladder, the adenomyomas contained more abundant lymphocytes than the uninvolved portions of the gallbladder. The lymphocytes were most numerous about the cysts. Intramural abscess or abscesses were encountered in 15 specimens (15 per cent); these were adjacent to the cysts. In 3 cases, intramural stones were present; they consisted of cholesterol clefts surrounded by distorted columnar epithelium and bile pigment.

**Clinical Picture:** The average duration of symptoms was three and nine-tenths years, the longest being twenty-five years and the shortest three weeks. In 74 cases (72 per cent), a history of cholecystic disease was elicited; the distressing symptoms were those already enumerated in the discussion of polypus. In 55 (53 per cent), a definite history of severe colic in the right upper quadrant of the abdomen, with or without extension of pain, was given. Twenty-five patients (24 per cent) had been jaundiced on one or more occasions, and on examination, 6 were icteric. Tenderness in the right upper quadrant of the abdomen was discovered in 38 cases (37 per cent).

Diagnosis: A diagnosis of cholecystic disease with or without stones was made in 72 (70 per cent) of the 103 cases. In 10 cases, a preoperative diagnosis of tumor of the gallbladder was hazarded by virtue of cholecystography. Of the laboratory procedures, cholecystography was the only one of aid in diagnosis. In 73 cases, reports of roentgen study of the gallbladder by the oral dye method were available. In 15 of the 73 (20 per cent), normal function without defects was reported; in 48 (66 per cent), some degree of impaired function or defects interpreted as stones or both were reported; in 10 cases (14 per cent), normal function of the gallbladder was reported, and, in addition, a defect in the shadow at the fundus was interpreted as tumor of the gallbladder. In each of these 10 cases the lesion was shown at operation to be adenomyoma.

Complications: Intramural abscess occurred in 15 cases (15 per cent); the abscess was discovered only at microscopic examination. Intramural stone occurred in 3 of the gallbladders. No malignant lesions were encountered.

The rarity of adenomyoma of the gallbladder is attested by all writers on the subject, the incidence given varying from 1 per cent in material examined at necropsy (Nicod) to 9.5 per cent in gallbladders removed at operation (King and MacCallum). In this group of cases, the incidence of adenomyoma is roughly about 1 tumor in every 100 gallbladders removed at operation. Nicod found adenomyoma of the gallbladder equally divided between the sexes; in this group, women predominated by 3 to 1 (77 women to 26 men); this could be due to the higher incidence of cholecystic disease in women.

The abundant evidence of chronic inflammation and stones found in this group of cases might be interpreted as favoring the roles of inflammation and the trauma of stones in the causation of adenomyoma as championed by Buzzi and Lascano Gonzalez, King and MacCallum, Kordenat, Lubarsch and Luschka; in almost every case, chronic inflammation was more evident in the adenomyoma than in the uninvolved portion of the gallbladder, which was as a rule itself chronically inflamed; in 15 per cent, inflammation reached the stage of formation of abscess. Stones were present in 60 per cent of the gallbladders. However, one must not overlook the surmise of both Eiserth and Nicod that this inflammation may be secondary to the tumor. There is also a selective factor in this group of cases; the gallbladders were removed in an effort to relieve the symptoms of chronic cholecystitis or cholelithiasis or both, and one must not underestimate the importance of the stones as a cause of the chronic inflammation seen.

There are several points in favor of the hypothesis that adenomyoma of the gallbladder is a congenital anomaly, as supported by Abell, Aschoff

and Bacmeister, Eiserth, Hromeda, Nicod and Ribbert. They pointed out that the constant location in the fundus, the site of other congenital malformations, such as congenital diverticulum, favors the hypothesis of embryonal origin; in this group of 103 cases, 96 of the tumors were confined to the fundus; in 5, the entire gallbladder was involved, and in only 2 was the tumor localized away from the fundus. In addition, the generalized tumors and the ones located away from the fundus were smaller tumors. On the other hand, in no section was any embryonal tissue seen nor is any described in the literature. Congenital anomalies usually are manifest in early life; the average age of this group of patients was 48.9 years. This is in agreement with the findings of Lubarsch whose patients' average age was 55 years and Eiserth whose patients' average age was 59 years. Congenital anomalies have the further characteristic of occurring in multiple locations. In this, as in Nicod's series, adenomyoma was the only tumor apparent; however, Eiserth found other benign hamartoblastomatous tumors in cases of adenomyoma of the gallbladder.

The pathologic characteristics of the tumors studied have been described already and are identical with the descriptions given in the literature, with two exceptions: first, in 6 cases there was considerable hyperplasia of the epithelial elements in a portion (usually central) of the tumor and, secondly, there was complete absence of any signs of malignancy. The absence of malignancy is in agreement with the findings of Chiray, King and MacCallum, Nicod and Wellbroch. On the other hand, Buzzi and Lascano Gonzalez, Eiserth and Pytel all stated that these tumors become malignant. Only Eiserth described a case of adenocarcinoma arising in an adenomyoma of the gallbladder.

There was no characteristic set of symptoms related to this tumor; this confirmed the experience of Abell, Buzzi and Lascano Gonzalez, Judd and Hoerner and Eiserth. Robson and Weidlinger both expressed the belief that adenomyoma might play some part in the production of pain by interfering with contraction of the gallbladder. The small size of the tumor and its position away from the cystic duct are probably the reasons for the lack of symptoms. In cases in which there is colic of the right upper quadrant of the abdomen but no pathologic condition other than chronic cholecystitis and adenomyoma, the possibility of a passed gallstone must be considered.

Complications: There were small intramural abscesses in 15 cases and intramural stones in 3. King and MacCallum and Schoenlank mentioned the possibility of rupture of the intramural abscesses into the peritoneal cavity with the development of peritonitis; in none of the 15 cases of abscess was peritonitis present. Prolapse of the tumor with obstruction of the cystic duct as described by Hromeda, King and

MacCallum and Klose and Wachsmuth was not encountered, nor had a portion of any tumor become detached, as mentioned by both Phillips and Risak.

#### FIBROMA

*Literature.*—Albers<sup>46</sup> found and reported a submucous fibroma of the gallbladder. Walthard<sup>47</sup> reported a similar case in detail: The wall of the gallbladder was thickened, and there were abundant signs of chronic inflammation. The gallbladder contained several pigment and cholesterol stones. The tumor involved most of the wall, the signs of chronic inflammation being greatest where the tumor was thickest. It consisted of fibroblastic cells with little cytoplasm; in places, the cells were so

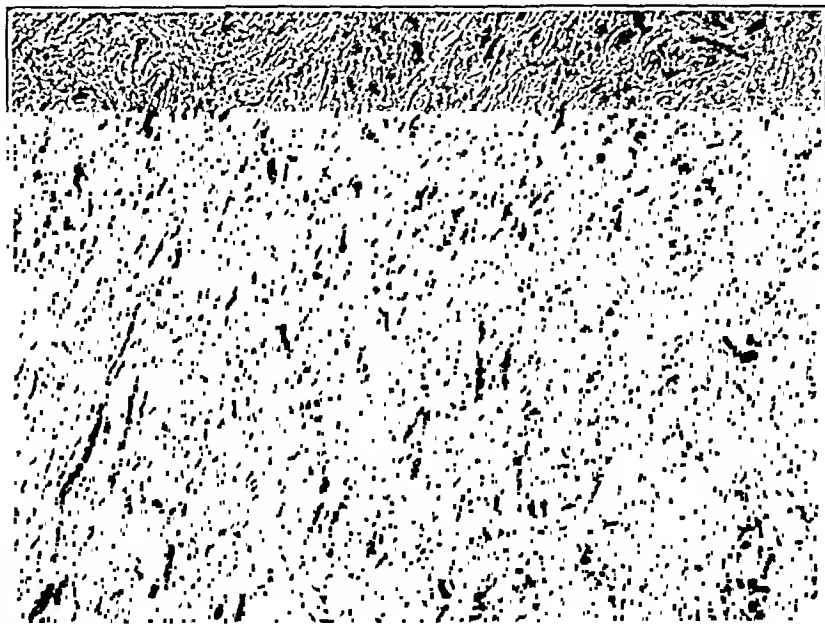


Fig. 3.—Fibroma of the gallbladder (stained with hematoxylin and eosin;  $\times 55$ ). Note large mononuclear cells that resemble ganglion cells. Cresyl violet and Bodian stains failed to reveal any nervous tissue.

numerous that the growth resembled sarcoma. At some points it simulated neurofibroma, but no nervous tissue cells were present. Walthard attributed the tumor to chronic inflammation.

*Findings.*—There were 2 cases of fibroma of the gallbladder; in both cases the tumor occurred at the fundus, and in both cases stones were

46. Albers, cited by Hanser, R.: Gallenblase und Gallenwege, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 5, pt. 2, pp. 748-860.

47. Walthard, B.: Ueber diffuse Fibromatose der Gallenblase, *Zentralbl. f. Chir.* 52:341-344 (Feb. 14) 1925.

present. One tumor was 8 and the other 12 mm. in diameter. One tumor was found incidentally in the gallbladder at operation for carcinoma of the stomach; the other occurred in a case in which the patient gave a history of attacks of colic in the right upper quadrant of the abdomen accompanied by acholic stools, dark urine, nausea, vomiting and jaundice. The cholecystogram showed a nonfunctioning gallbladder.

In both cases there was ulcerative cholecystitis. The tumors extended from the mucosa to the serosa and consisted of relatively acellular white fibrous connective tissue. Scattered through both tumors were a few lymphocytes. One tumor contained many mononuclear giant cells with pseudopods that gave them the appearance of nervous tissue cells similar to anterior horn cells; however, cresyl violet and Bodian stains showed that they did not originate from nervous tissue (fig. 3).

The 2 cases encountered are like Walthard's in that in both the gallbladders contained stones and the tumors were infiltrated by lymphocytes. In no portion of either tumor was there the sarcoma-like cellularity that he described. It is interesting that he mentioned that at first glance the tumor resembled neurofibromatosis of the skin, for in 1 of the cases already described there were many large cells that resembled nervous tissue cells; however, cresyl violet and Bodian stains disproved an origin from nervous tissue, and the cells were probably mononuclear giant cells. The location of both tumors in the fundus speaks for their being congenital, but the abundant signs of chronic inflammation are in favor of the inflammation as the stimulus to growth of fibrous tissue. Like adenomyoma and polypus these tumors showed no characteristic clinical picture.

#### SUMMARY AND CONCLUSIONS

On the basis of a review of the literature and a study of 150 cases of benign neoplasms of the gallbladder encountered at the Mayo Clinic from Jan. 1, 1906, to Dec. 31, 1938, inclusive, the following conclusions were drawn:

The benign neoplasms of the gallbladder are polypus, adenomyoma and fibroma; they usually occur in the middle decades of life.

Benign neoplasms of the gallbladder are rare. Polypus and adenomyoma each occur once in roughly every 100 gallbladders removed at operation.

Chronic inflammation is the constant concomitant of benign neoplasms of the gallbladder, particularly when stones are present. Cholelithiasis is frequently present in the gallbladder bearing a benign neoplasm. Chronic inflammation and the trauma of gallstones probably play a role in the causation of benign neoplasms of the gallbladder. However, congenital misplacement of tissue may be an additional factor in the causation of adenomyoma of the gallbladder.

No characteristic clinical picture is exhibited by these tumors; the symptoms and the physical findings are those of the concomitant chronic cholecystitis or cholelithiasis or both. The only means of preoperative diagnosis is cholecystography.

The incidence of malignant changes in these neoplasms is low; two malignant lesions (in the same gallbladder) occurred in 45 cases of polypus of the gallbladder; no malignant lesion was discovered in 103 cases of adenomyoma of the gallbladder or in 2 cases of fibroma of the gallbladder.

Intramural abscess and intramural gallstone occur as complications of adenomyoma of the gallbladder.

The possibility of malignant change or complications, such as intramural abscess, as well as the constantly present chronic inflammation and the frequently present gallstones calls for the removal of gallbladders containing a benign neoplasm.

# COUP-CONTRECOUP MECHANISM OF CRANIO-CEREBRAL INJURIES

## SOME OBSERVATIONS

CYRIL B. COURVILLE, M.D.

LOS ANGELES

No other subject in the realm of disorders of the central nervous system offers more immediate rewards to study or is more timely than injuries of the brain. This is particularly true at present with practically the entire world committed to war. With the emphasis now being placed on motorized and mechanized warfare, a soldier is now about as apt to sustain an injury to the head from a "traffic" accident as he is from bullets or fragments of high explosive shell, at least insofar as injuries minor enough to permit the patient to reach trained medical attendants are concerned. It is therefore apropos in this discussion of injuries of the brain to review once more that intriguing problem of the mechanism of coup-contrecoup traumatisms of the brain, once the catchword of every junior medical student but now almost completely forgotten in the rush of matters of more immediate clinical concern. It is the purpose of this paper to reopen the subject of "closed injuries" of the brain, to consider their basic mechanism and to draw a few conclusions which seem to be of clinical importance.

## HISTORICAL NOTE

The term contrecoup, while commonly used, has a none too certain history. It was introduced by a group of French surgeons (who were responsible for the famous "Memoirs of the Royal Academy" and of whom Louis was an outstanding exponent) in the latter half of the eighteenth century, although injuries of the brain on the side opposite the point of impact were first recorded by Fallopius in the latter part of the sixteenth century and by Valsalva in 1700. The term was intended to signify an injury (contusion) of the brain at a point opposite to that sustaining the impact of the blow. Such lesions were probably common enough, for the term is constantly encountered in the surgical literature of the nineteenth century, particularly the latter half. The philosophy originally proposed was essentially the correct one, i. e., that oscillations of the brain set up at the point of impact traverse the skull and injure the brain by local vibrations against the inner table of the

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skull. Because, however, this theory could not account for fractures of the skull, it was replaced by one suggested by Bruns, which explained the presence of these contusions by a temporary change in the form of the skull. This theory, closely tied up with the mechanism of bursting fractures, evidently held sway for many years, and even as astute an observer as Cushing was influenced by it.<sup>1</sup> As far as I have been able to determine, it was LeCount and Apfelbach<sup>2</sup> who added the concept that the head must be in motion to account for these contrecoup contusions. It is the object of this study to show that the original concept of transmission of force through the brain, rather than any bending or bursting effect on the skull, is probably the correct explanation of the lesion, and that the location and the nature of lesions produced by this mechanism are actually to be explained by the anatomic conformation of the skull and the relation of the cranial cage to the brain.

#### SURVEY OF SOURCE MATERIAL

This study is based on a review of 206 consecutive cases of fatal injury of the brain in which contusion of the brain sustained while the head was in motion was found. The details on which this study is based were sifted out of longer records in the Cajal Laboratory by two of my former students, Drs. Ernest M. Stanton and Lester S. Gale, and were included in an earlier survey of craniocerebral trauma.<sup>3</sup> Some few additional cases of diffuse contusion of the occipital lobe<sup>4</sup> and traumatic intracerebral hemorrhage<sup>5</sup> (which have been described in other contributions) also have been included in this survey. All of the patients sustained their injuries as the result of automobile collisions, by being struck by a motor vehicle or a train, or as the consequence of falls. Of this number, 179 (87 per cent) of the persons were males; 27 (13 per cent), females. The incidence of fatal cases in the ten decades of life, was respectively, 15, 15, 20, 28, 48, 31, 26, 17, 1 and 1. Of the 202

1. Cushing, H.: *Surgery of the Head*, in Keen, W. W.: *Surgery: Its Principles and Practice*, Philadelphia, W. B. Saunders Company, 1919, vol. 3, pp. 69 and 70.

2. LeCount, E. R., and Apfelbach, C. W.: *Pathologic Anatomy of Traumatic Fractures of Cranial Bones and Concomitant Brain Injuries*, J. A. M. A. **74**:501 (Feb. 21) 1920.

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cases in which the survival period was known, death occurred on the first day in 69 cases (34.1 per cent); on the second day in 23 cases (11.3 per cent); on the third day in 20 cases (9.9 per cent); on the fourth day in 12 cases (5.9 per cent); on the fifth and sixth days in 7 cases each (3.4 per cent), and on the seventh day in 5 cases (2.4 per cent). Death came in the second week in 32 cases. The remaining 27 patients (13.6 per cent) survived more than two weeks.

In order of frequency, the location of scalp wounds (indicating the area which received the brunt of applied force) was parietal in 57 cases, occipital in 52 cases, frontal in 43 cases, temporal in 35 cases, vertical in 4 cases and either unknown, not stated or not evident in 15 cases. The common sites for cerebral contusion were as follows: the temporal lobe in 145 cases (the dorsolateral and inferior surfaces in 101 cases and the temporal pole in 44 cases) and the frontal lobe (chiefly the basilar surface) in 84 cases.

On analyzing the various special situations, certain important deductions regarding the mechanism of coup-contrecoup injury of the brain were made possible. A brief survey of these data is therefore in order. Contusions, abrasions and lacerations of the frontal scalp, indicating that the projected head had met with some immovable or relatively immobile object in this region, were found in 43 cases. In this group the frontal lobes alone were contused in 26 cases, the temporal lobes alone, in 11 cases, while both the frontal and the temporal lobes were affected in 6 cases.

Traumatic lesions of the occipital scalp were present in 52 cases. In 51 of these cases, the cerebral lesions were obviously contrecoup, the frontal lobes (21 cases), the temporal lobes (14 cases) or both (16 cases) being the seat of the contusions. In 1 case, a parietal contusion was due to depressed skull fracture, therefore a direct lesion, and in another, in which contrecoup temporal contusions also were present, a severe occipital contusion resulted from a depressed skull fracture, also a direct lesion.

Parietal and temporal scalp injuries, indicative of a lateral projection of the head, were found in 92 cases (largely or exclusively parietal in 57, and largely or exclusively temporal in 35). In the parietal group, the major cerebral contusions were contrecoup in 49 of 57 cases. The dorsolateral and inferior surfaces of the temporal lobes alone were affected in 31 cases, the middle portion of the lobe being predominantly contused. The basilar surfaces of the frontal lobes were exclusively affected in 9 cases. Both the frontal and the temporal lobes were contused in 6 cases. In 2 cases, the opposite parietal lobe seemed to be predominantly affected, and in 1, the occipital lobe was contused, obviously not a coup-contrecoup effect of a parietal injury. In 8 cases, the chief contusions seemed to be

on the side of the injury. The parietal lobe was contused in 3 cases; the temporal lobe, in 1; the frontal lobe, in 1, and both the frontal and the temporal lobes, in 3 others.

In the group with scalp injuries predominantly temporal in location (35 cases), the major cerebral contusion was contrecoup in 24 cases. A direct or coup contusion also was present in 7 cases. The inferolateral surface of the temporal lobe was the seat of the contusion in 20 cases; the basilar surface of the frontal lobe, in 3, and both the frontal and the temporal lobe, in 1 additional case. In 11 cases, the major contusion was a direct or coup lesion, probably due to local severe fractures in at least 7 of this group in which such fractures were evident. Some of the contusions had to be explained otherwise, however, for the lesions in some instances were typical of the coup-contrecoup mechanism. The homolateral temporal lobe was affected in 6 cases; the frontal lobe, in 3 cases; both lobes, in an additional case, and the parietal lobe in 1 case.

In 4 cases of scalp injuries of the vertex, the essential (contrecoup) contusion was in the basilar frontal region in 3 cases, and in the anterior temporal lobe, in 1 case.

#### PATHOLOGIC DEDUCTIONS

On the basis of observations made in this group of cases and in another group of traumatic intracerebral hemorrhages, the following deductions were made, which will serve as a basis for a discussion of the mechanism of coup-contrecoup lesions of the brain.

1. When the projected head strikes in the frontal region, coup contusions of the basilar surface of the frontal lobe, or, less often, of the anterior portion of the temporal lobe or of both tend to be present. Contrecoup lesions of the occipital lobe are never produced by this mechanism.

2. When the projected head strikes in the occipital region, contrecoup contusions of the subfrontal or, somewhat less often, of the anterior temporal region or of both is the rule. A coup, or direct, lesion results only from a local depressed fracture of the skull.

3. In either event, the frontal or the temporal lobe opposite to the area of impact is predominantly affected. The nearer the midline of the head is to the application of force, the more likely will be the bilaterality of the lesion, particularly of a major one.

4. When the falling head strikes in the occipital region to produce a linear fracture which extends down into the posterior fossa toward or near the foramen magnum, a direct or coup contusion of the adjacent inferior surface of the cerebellum almost invariably results. As will be explained later, linear fractures of the vault rarely produce underlying contusions; similar fractures of the base of the skull are more likely to do

this. Contrecoup contusions of the contralateral or bilateral subfrontal (and often anterior temporal) regions likewise are almost always a concomitant lesion.

5. When the projected head strikes on its side (i. e., the temporal or parietal regions), the major contusion is a contrecoup one, affecting the opposite temporal lobe, usually the inferolateral surface. Involvement of the adjacent frontal and parietal areas (superficial contusion) also may occur with purely lateral applications of force. Smaller coup lesions also may be found, but they occur in only a small proportion of the cases.

6. When the projected head strikes on the central vertex, the line of force being directed forward, contrecoup contusions of the subfrontal or anterior temporal regions are the rule.

7. When the moving head strikes at the vertex or the high parietal region, the line of force being directed backward, a relatively rare type of contusion (diffuse contusion) may result on the medial or the lateral surface of the temporo-occipital region—a homolateral but contrecoup effect. It is probably to be accounted for on a vascular basis.

Since these lesions consistently occur as just outlined, they may be taken as a basis for an analysis of the mechanism of coup-contrecoup injuries of the brain. Apparent exceptions, as a rule, can be accounted for on the basis of the effect of severe fractures, usually depressed, with local injury of the subjacent portion of the brain or on the basis of multiple applications of force by this or some other mechanism.

While in this study chief attention is being paid to contusions of the brain, it is well to remember that in some cases subdural hemorrhages and hematomas and more often gross intracerebral hemorrhages and even petechial hemorrhages are to be included in the group of lesions of the brain resulting from the coup-contrecoup mechanism.

#### APPLIED ANATOMY

For the purposes of this study, the interior of the skull above the tentorium may be considered as a hemisphere, the interior of which is marked only by slight irregularities, most marked in its inferior and anterior reaches. Even these irregularities are modified by being smoothly covered by the dura mater. The dome-shaped calvarium is partially divided by the falx cerebri, beneath the arch of which there is free communication from one side to another. This communication permits of a certain amount of dislocation of the nervous tissues from side to side. It is likely that it is this increased mobility of the central or ganglionic portion of the brain which makes traumatic injury of these parts by this mechanism a practically unheard of complication.

The base of the skull stands out in contrast to the relatively smooth vault by the presence of its major and minor irregularities. The major

irregularities are the three cranial fossae on either side, the separating borders of which are the sharp sphenoid and petrosal ridges. The anterior fossa is marked by a slightly irregular central eminence or dome, the roof of the orbit which is formed by the thin orbital plates of the frontal bone. Not only because they are thin but also because they are arched, these plates may be fractured by contrecoup force. The weight of the nervous tissue driven downward against these small domes as the result of severe force produced by falls on the upper and posterior part of the head is sufficient at times to result in eggshell fractures of this plate. Such fractures in turn result in traumatism of the orbital tissues sufficient to produce, and often responsible for, hemorrhage manifested by the "owl eye" of the injured patient.

The dome of the orbital plate is surrounded in front and laterally by a groove the paramedian portion of which, lying over the cribriform plate, is deeper than is usually appreciated. It is separated from its fellow of the opposite side by the crista galli. It is the depth of this sulcus, together with the irregularity of its walls, which contributes largely to the common median subfrontal contusions, which so often involve the olfactory bulb. It is the more shallow lateral groove which accounts for the inferolateral tears which often initiate one type of traumatic intrafrontal hemorrhage.

The middle fossa is a rounded depression, the floor of which is marked by fairly deep convolutional grooves which course antero-posteriorly but which tend to fade out posteriorly and over the lateral wall of the fossa. The anterior portion of the fossa is overhung by the sphenoid ridge, making a bony pocket from which the temporal pole can scarcely escape from the effects of either frontal or occipital collisions. The floor of the middle fossa is continuous posteriorly with the smooth upper surface of the tentorium.

The anatomy of the posterior fossa is of relatively little importance in a discussion of coup-contrecoup injuries, for when severe force is applied to this part of the cranial basis, death is likely to result owing to the effect of shock on the vital centers. The nonfatal effects of trauma applied by this mechanism to the occipital bone result in but one outstanding lesion—a linear vertical contusion of the adjacent ventral surface of the cerebellar lobe, an immediate consequence of linear fractures of the squamous portion of the occipital bone which run downward and forward into or near the foramen magnum.

These essential anatomic details are shown in the accompanying photographs of the base of the skull (fig. 1).

The peculiar relations of the brain to the cranium which are of primary importance in this connection should be briefly noted. In general, the more irregular the bony walls of the skull are and the more

completely the portion of the brain concerned is enveloped by them, the more likely it is that that part is to sustain coup or contrecoup contusions. Further, the peculiar type and distribution of the contusions are directly dependent on the contour and elevation of the adjacent bony walls.

The attachments of the brain also play a definite although much less conspicuous part in the production of the ultimate lesion. The relative fixation and rigidity of the upper medial border of the cerebral hemispheres due to fixation by the exits of the superior cerebral veins to the falx at the superior longitudinal sinus, more than likely account for the comma-shaped petechial, or even larger, hemorrhages (the result of tearing of small subcortical venous radicals) which are not infrequently found in the adjacent cerebral centrum, particularly in the frontal lobes.

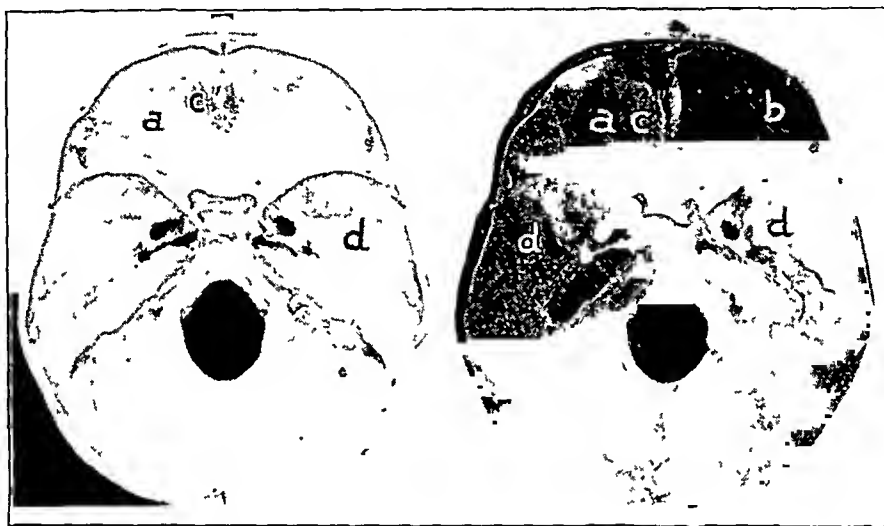


Fig. 1.—Anatomic picture of the base of the skull showing, by lights and shadows, the dome of the orbit (*a*) with its shallow lateral groove (*b*) and the deeper medial (olfactory) groove (*c*), as well as irregularities on the floor of the middle fossae of the skull, which are here thrown into relief (*d*).

While the attachments of the brain to the cranial basis incident to the passage of the nerves do not contribute so definitely to the production of gross lesions, such attachments do promote a considerable intimacy of the nervous and bony tissues which favors the production of local contusions by linear fractures. While this development is not so common in the anterior and middle fossae of the skull as in the posterior ones, it does occur and thus alters the pathologic picture resulting from the coup-contrecoup mechanism.

*Relation of Fractures to Contusions of the Brain.*—It is necessary at this point to consider the relation of fractures of the skull to injury of the

brain, a relation which has been considerably overemphasized in an era not entirely past. There are certain matters pertaining to fractures and their influence on the pathologic picture which follows injuries sustained with the head in motion which here need to be underscored. In the first place, the location of the fracture tends to indicate the point of application of maximum force and therefore should suggest the line of transmission of force and its consequences. For example, a linear fracture of the occipital bone sustained in a fall should suggest the likelihood of a cor-

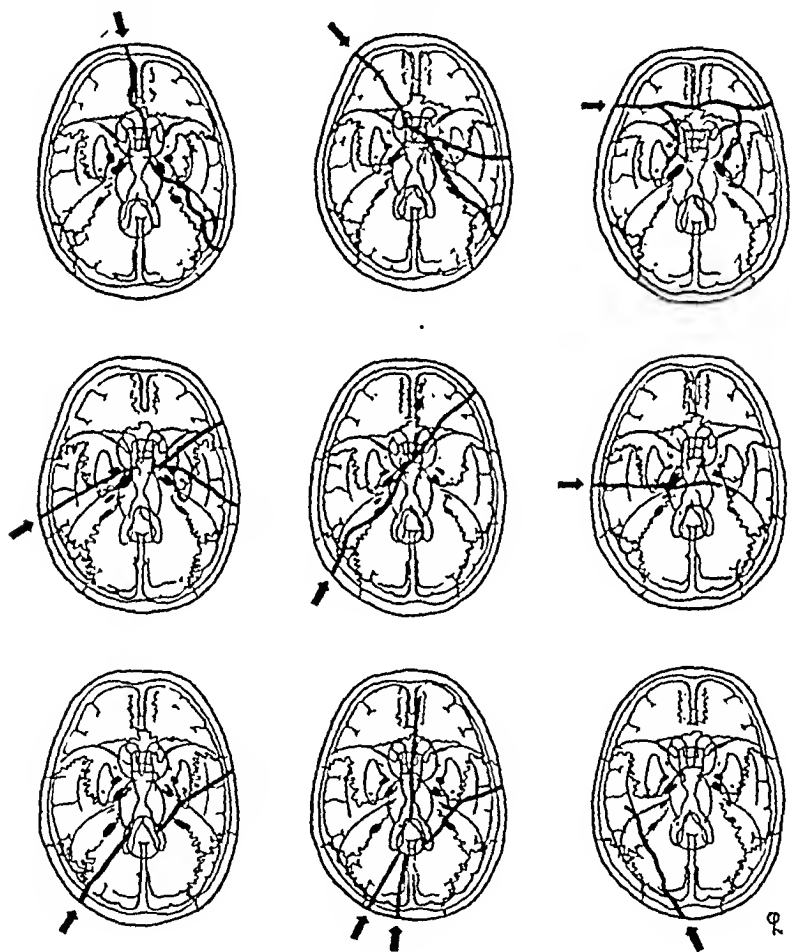


Fig. 2.—Diagrammatic representation of the course of fracture lines through the cranial basis, showing how such fractures serve as an index of the direction of applied force (adapted from Rawling, L. B.: *The Surgery of the Skull and Brain*, London, Oxford University Press, 1912, pp. 85-88).

responding coup cerebellar contusion and contrecoup contusions of the subfrontal and temporal polar regions of one or both sides. It also is necessary to remember that multiple fractures of the skull may indicate multiple sites of application of force with consequent multiplicity of mechanisms of cerebral injury.

Secondly, the direction of the fracture line generally shows the direction of the traumatizing force, although this line of the fracture may be influenced somewhat by the peculiar anatomic relations (e. g., buttresses, basilar foramina) of the portion of the skull affected. Nevertheless, by a study of many instances this point is sufficiently well established to say that the direction of the fracture line is definitely useful in evaluating the consequent damage to the brain. This principle is illustrated in figure 2.

For the reasons outlined, it is obvious that linear fractures of the cranial basis are much more apt to produce contusions of the brain than linear fractures of the vault. Only rarely does a linear fracture of the vault produce such a contusion and then only when it is unusually long,



Fig. 3.—Diagrams showing the effect of a fall on the back of the head; *A*, coup contusion of the adjacent right cerebellum and contrecoup contusion of both the subfrontal and the left anterior temporal regions; *B*, diffuse contusion (contrecoup) of the median temporo-occipital cortex.

sufficiently so to permit transitory dislocation against the brain of the bone forming one margin of the fracture. Fractures of the anterior and middle fossae do not necessarily produce a contusion by themselves unless severe or accompanied by displacement of bony fragments. In my experience, fractures which cross these fossae transversely are much more apt to produce contusions than those which course anteroposteriorly. This is probably to be explained by the naturally greater transverse irregularity of these fossae.

As has already been mentioned, vertical linear fractures of the occipital bone are especially prone to produce contusions of the cerebellum, so much so that such fractures should make one presume the



likelihood of such a contusion (fig. 3A). Fortunately, the clinical effects are transitory, owing to the recoverability of cerebellar function.

In this consideration, we are not including compound comminuted depressed fractures, the traumatizing effect of which on the underlying brain is a foregone conclusion. It should be definitely restated that even those contusions consequent to linear fractures are purely incidental. Contusions of the brain characteristic of the coup-contrecoup mechanism of injury are entirely independent of fractures of the skull. Moreover, the great majority of fractures are, in and of themselves, unaccompanied by any direct effect on the brain. Finally, it should be remembered that the most serious immediate result of fracture is the laceration of meningeal vessels (less commonly, of the dural sinuses) with extradural or subdural hemorrhage or the creation of avenues of infection (and/or air) into the intracranial chamber.

#### BASIC CONCEPTS

It should now be recognized, even by superficial students of the subject, that every type of trauma to the brain produces its own peculiar train of lesions. For example, it is not profitable to compare the pathologic effects of birth injury with those of "punch drunk" persons because of the wide diversity of their individual effects. Nor can one adequately interpret the characteristic effects of a gunshot wound of the brain with injuries consequent to falls or traffic accidents. When one undertakes to study the lesions of the so-called closed injuries, that is, those which may occur independent of any fracture, one should be prepared to visualize a group of lesions peculiar to the coup-contrecoup mechanism, developed as an immediate or, at times, delayed consequence of head injury sustained while the head is in motion.

In order to lay the requisite basis for discussion of the possible mechanism of coup-contrecoup lesions, a group of postulates is herewith presented:

1. The group of lesions recognized to be due to the coup-contrecoup mechanism occur only when the moving head strikes a stationary or relatively stationary object.

2. These lesions are the direct result of a peculiar application of force to the head and, as a general rule, are not due to fractures of the skull, although they may be modified, altered or complicated by such fractures.

3. The nature and the location of the resultant lesion are dependent on the anatomic relation of the injured part to its bony covering. The lesion may occur beneath the point (or area) of impact (coup lesion) or on the side of the brain diametrically opposite the point (or area) of impact (contrecoup lesion).

4. Other factors being equal, the extent of the injury is proportional to the force with which the head is projected against the traumatizing object.

5. Contrary to previously expressed theories, contrecoup injuries are the result of the transmission of force through the tissues of the brain, bruising the opposite cortex against the irregular internal surface of the skull.

6. The line of force is a straight one, unless deflected or interrupted by intervening structures of different consistencies.

7. The consequent lesions of this mechanism are not necessarily identical, there being interposed in some instances a personal factor. This factor consists chiefly of personal differences in vascular resiliency (turgor, strength, flexibility), although differences in the intensity of the force, the area of the head primarily affected by it and the direction in which it was applied probably account for much of the variation in severity of the lesion.

With these observations as a point of departure, a more critical analysis of each point will be undertaken.

#### INJURY TO THE PROJECTED HEAD

The essential difference in an injury to the brain sustained as a result of the coup-contrecoup mechanism as compared with blows to the head lies in the fact that when the head in motion strikes an immobile or relatively immobile object, the entire brain is affected by the shock; on the other hand, when the head is struck by a moving object, waves of force radiate only from the point of impact and diffuse out into the adjacent tissues. Because of the difference in density of the skull and dura as compared with that of the underlying brain, the violence of these waves of force is considerably lessened in crossing the subdural and subarachnoid spaces. It is also likely that the curved vault of the skull serves to diffuse considerably any force applied to it. While it is possible for a focal blow to derange cerebral function to the extent of producing unconsciousness, it may be taken as a rule that gross damage to the brain will not thus be produced unless the skull is fractured and the depressed fragments of bone act as a new traumatizing agent.

This situation is modified, of course, in the case of gunshot wounds. A bullet is propelled with a high degree of force and penetrates the cranial vault at a given point, often with relatively small bony damage. In addition to the lacerating effect of the missile itself, the brain often suffers from a severe degree of shock incident to the waves of force thrown off by the bullet, which waves vary in intensity with the velocity of the missile. This shock may result in coma or even immediate death.

The traumatic action of the indriven fragments of bone is usually limited, with rapidly diminishing effect. The immediate effects of the bullet itself are therefore due not only to the damage along its track incident to laceration of the nervous tissue and the blood vessels but also to the expansile force of the waves of pressure thrown off in its passing. The devastating possibilities of this second effect were recognized in the experiences of the first World War, when the entire skullcap and contained brain were found to be blasted off by the passage through the base of the skull of a rifle bullet fired at close range.

To get back to the subject, the contact of the head in motion with a stationary or relatively stationary object seems to add a new and different factor to the problem. The head itself becomes the missile, and the line of its trajectory becomes projected intracranially by a line, often broken or incomplete, of lesions of the brain. Just how these lesions are produced, remains to be shown.

#### "CLOSED" INJURIES OF THE BRAIN

The lesions of the brain which follow the coup-contrecoup mechanism are essentially the result of force applied to the "closed" or unbroken skull, although, of course, the picture may be modified or complicated by an overlying fracture. Nevertheless, the group of lesions herein considered is the direct consequence of a special application of force supplied by the moving head striking against a stationary or relatively stationary object. It is this important fact which must be borne in mind in evaluating the pathologic picture.

Not always so easy to evaluate, however, are cases in which multiple mechanisms of injury have been present. A person might sustain a primary frontal injury by being thrown against the windshield in an automobile collision and a secondary parietal injury by being thrown against the door of the car as the machine turns over. It is possible for this secondary injury to result in widespread superficial contusion. If the patient survives his injury, the secondary contusions, by production of motor symptoms (convulsive seizures), may be of greater clinical significance than the primary ones, which may have resulted in impairment of the sense of smell.

#### IMPORTANCE OF RELATIONS BETWEEN THE SKULL AND THE BRAIN IN THE PRODUCTION OF COUP- CONTRECOUP LESIONS

It is an important truism that, next to the mechanism of the head in motion, the peculiar anatomic relation between the skull and the brain is the most important factor in the production of gross lesions. The anatomic basis for this postulate has already been discussed in some

detail. If it were simply a matter of the brain moving within the skull, as has previously been postulated, a contusion of the brain would always result on the same and opposite sides of the brain. But such is not the case.

A simple example will make this point clear. When the projected head strikes with sufficient force in the right frontal region, right frontal contusion (coup lesion) will result, but there will be no contrecoup contusion in the left occipital region. Conversely, when a falling head strikes with sufficient force in the left occipital region, no direct or coup contusion results, but contrecoup contusion of the right subfrontal area results. In the first, the subfrontal lesion is coup; in the second, contrecoup, and in neither case is an occipital contusion produced.

The explanation of the predominant localization of contusions in the subfrontal and inferolateral temporal regions of the brain, whether coup or contrecoup in causation, seems to be found in the relation of the brain to the enveloping skull in these regions. The tips of the frontal and temporal lobes lie enclosed in a bony pocket the walls of which present considerable irregularity. Contusions of the lateral aspects of the brain, such as result from a lateral projection of the head, are always more superficial and widespread because no marked irregularities of the bony wall are here present. The occipital lobe is bounded on two of its three surfaces by the falx cerebri and the tentorium, the smooth and curving surfaces of which, as well as their relative resiliency, seem sufficient to prevent gross injuries to the brain in this region.

#### PARALLELISM OF DEGREE OF FORCE AND SEVERITY OF LESION

The postulate that, other factors being equal, the severity of the lesion is proportional to the degree of force with which the head is projected against an object seems self explanatory. It is therefore necessary only to emphasize certain important clinical features that this point is considered. In the first place, some estimate of the severity of the contusion may be gained from the duration of the preliminary coma. From a study of cases in which there was injury to the head but in which death actually resulted from other traumatic lesions, it has been learned that contusion of the brain is not likely to exist unless the person has been unconscious for approximately six hours. In other words, it takes a shocking force sufficient to result in a six hour coma to produce contusion of the brain. Shorter intervals of coma may, however, be coexistent with contusions of the brain in children. In 1 case, it was insisted by the parents that a Mexican boy was never unconscious after a fall from a building, and yet at autopsy some years later a moderate-sized healed contusion of the temporal lobe was found. On this basis, in the majority of patients with prolonged coma not due to other causes than the shock itself and in

whom the coup-contrecoup mechanism has taken place, contusion of the brain has probably been sustained.

From another viewpoint, the finding of contusion at autopsy months or years after an injury should enable one to estimate the severity of the injury as well as the part of the head which sustained the injury.<sup>6</sup> By interpreting the evident facts in the light of what is known about the mechanism of coup-contrecoup injuries, the picture of the original trauma can be reconstructed, at least in its general outlines.

#### THE ESSENTIAL MECHANISM OF COUP-CONTRECOUP INJURIES OF THE BRAIN

The interesting phenomenon of contrecoup injuries has long intrigued the curious clinician. Two theories have been proposed to account for it. One school postulated that the contrecoup injury is due to the fact that the skull acts much like a hoop which has been struck on one side, that is, the opposite side approximates the struck side. Forgetting for the moment that the solid base of the skull precludes any close comparison between the cranial vault and a hoop, the fact that injuries to some areas produce only coup lesions and to others only contrecoup ones seems to indicate that some other factor is responsible for the cerebral injury.

A second theory of coup-contrecoup injuries stated that the lagging brain within the moving skull sustains a contrecoup bruise when the skull is suddenly stopped in its flight by collision with some stable object. The fact that the opposite side of the brain is not invariably injured under such circumstances again seems to nullify this presumption.

What mechanism, then, does account for the peculiar group of lesions following injury to the moving head?

My concept of the mechanism of coup-contrecoup injuries is a relatively simple one and is an extension of the philosophy of the mechanism of gunshot wounds of the brain:

1. The head in motion corresponds to a bullet in flight, both describing a line of force in their trajectory.
2. With the abrupt cessation of the trajectory by the collision of the head with an immobile or relatively immobile object, the line of force is

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6. It has been my practice, for the benefit of those attending my neuropathologic clinics, to predicate the seat of the injury to the scalp and the skull as well as to estimate the severity of this injury on the basis of the location and the size of the old contusions which are found in the brains of patients who survived these lesions for a considerable time and who died of another cause. In a number of instances, the record of the previous injury is often available for study, since the patient has been hospitalized in this institution. The ability to interpret the mechanism and the severity of the injuring force with reasonable accuracy indicates that the essential philosophy of this paper at least approximates correctness. This has been substantiated in well over 100 old traumatic lesions of the brain studied by me.

suddenly reversed and extends backward through the nervous tissue to the opposite side of the skull.

3. This line of force,<sup>7</sup> a continuation of the line of trajectory of the head, is a relatively straight line if the trajectory of the head was at right angles to the surface struck. If not at right angles, there is an increasing deflection on the curved surface of the head until a point is reached where the intracranial contents are not grossly affected.

4. This line of force extends to the opposite side of the skull, presumably with waves of force spreading out from it.

5. This force travels by continuity through the nervous tissue and probably through the fluid in the ventricles as well.

6. It may be deflected or diffused to some extent by contact with, or interruption by, structures of different densities, such as the falx cerebri or the tentorium.

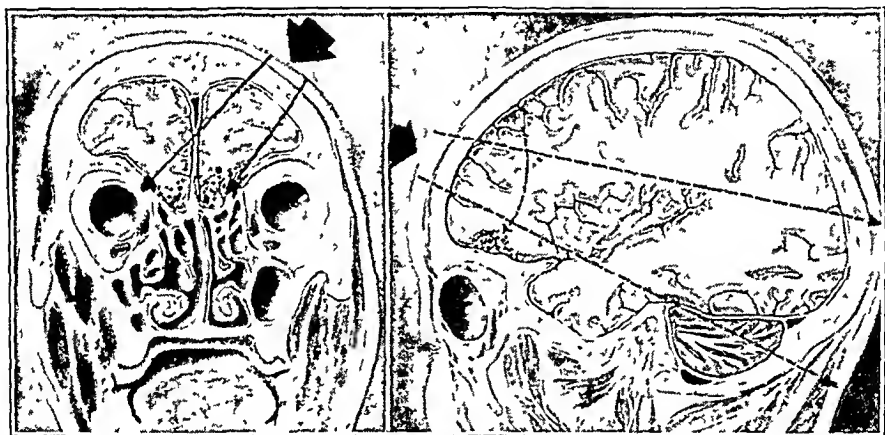


Fig. 4.—Diagrams illustrating subfrontal coup contusion, showing the mechanism of its production.

7. The ultimate lesion depends on the relation of the waves of force along this line to the cortex and the subcortex which lie against the inflexible bony wall, on the degree of resilience of the blood vessels in the areas affected by the waves of force and on the anatomic structure of the brain in the area involved.

The observations which seem to support this theory of coup-contrecoup injury are numerous but evident only on close analysis of the facts. In the first place, it seems clear that there is a line of force; this is

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7. The term "line of force" is used in this study in a general sense. Strictly speaking, it is more than a line—otherwise the contrecoup injury would be extremely minute. It is more likely a wave of force which dislocates the nervous tissue along a line with progressive diminishing effects on all sides as the line is deviated from.

evidenced by the relatively localized character of the contrecoup lesion. Diminishing waves of force from the point of a blow as on the stationary head should produce lesions diminished in magnitude from the point of contact and should be completely diffused by the time the opposite wall of the skull is reached. In other words, the same type of lesions would be produced in both cases if the mechanism were the same. Further evidence that this force travels in a line is the occurrence in the frontal and temporo-occipital centruns of intracerebral hemorrhages on the basis of this mechanism. This mechanism also explains the chain of petechial hemorrhages occasionally found under similar circumstances. The same is true also of the chain of transverse ganglionic hemorrhages after lateral projection of the head, the larger lesion being contrecoup.

That the most serious lesions are not necessarily produced along this line of force in the nervous tissue but are dependent on local bony relations is evident from the location of coup lesions following frontal injuries. Since the force of the blow is usually sustained in the frontal area, if the blow itself were primarily responsible for the contusion, such a contusion should be dorsolateral or at least polar in location. But it is not. It is found at the base of the frontal lobe, where deflected waves of force thrust the cortex against the uneven surface of the olfactory groove (fig. 4).

#### DEFLECTION OF THE LINE OF FORCE

That a certain amount of diffusion or deflection of the line of force may occur is suggested by the fact that groups of small petechial hemorrhages may be present at the genu and the splenium of the corpus callosum where these lie in contact with the falx cerebri. The yielding nervous tissue meets the relatively resistant falx, and laceration of the small regional blood vessels results. However, this deflection is rarely sufficient to disturb the distribution and the character of the essential lesions which follow this type of injury.

#### THE SIGNIFICANCE OF THE DISTRIBUTION AND THE NATURE OF COUP-CONTRECOUP LESIONS

Some of the more general postulates now having been considered, attention can be directed to the immediate gross effects of trauma to the brain and the mechanism of their production on the basis of this thesis. Attention will be given (1) to the effects of the application of force in the various portions of the head and (2) the significance of the various lesions produced.

*Application of Force in Relation to the Curvature of the Skull.*—It seems self evident that if the projected head strikes a solid object on a line oblique to the curved dome of the skull, the force is diffused in

and absorbed by the scalp and the skull in such a way as to prevent notable intracranial damage. Such applications of force are manifested clinically by brush burns or more serious abrasions if superficial or by avulsions of the scalp and erosion of the outer table of the skull if



Fig. 5—Diagrams showing. *A*, symmetric coup subfrontal and parasylvian contusions due to midfrontal injury; *B*, homolateral coup subfrontal contusion due to oblique lateral frontal injury; *C*, symmetric contrecoup subfrontal contusions due to midoccipital injury; *D*, contrecoup subfrontal contusions due to oblique lateral occipital injury.

more profound. The more nearly vertical the line traveled by the projected head is relative to the point of impact, the more likely it is that



coup or contre-coup injuries will result. The line or wave of force will thus be projected across the vault of the skull forcing the brain against the opposite side of the curve of the vault with resultant contusions.

Considering the skull in its horizontal section, the point of the application of force decides the symmetry or asymmetry, the homolaterality or contralaterality of the site of the lesion. When the moving head strikes directly in the frontal or the occipital midline, the contusions of the subfrontal and anterior temporal regions are about equal in size and symmetrically placed. If, on the other hand, the blow is sustained in a paracentral but directly frontal or occipital position, the largest subfrontal and anterior temporal contusions are usually found

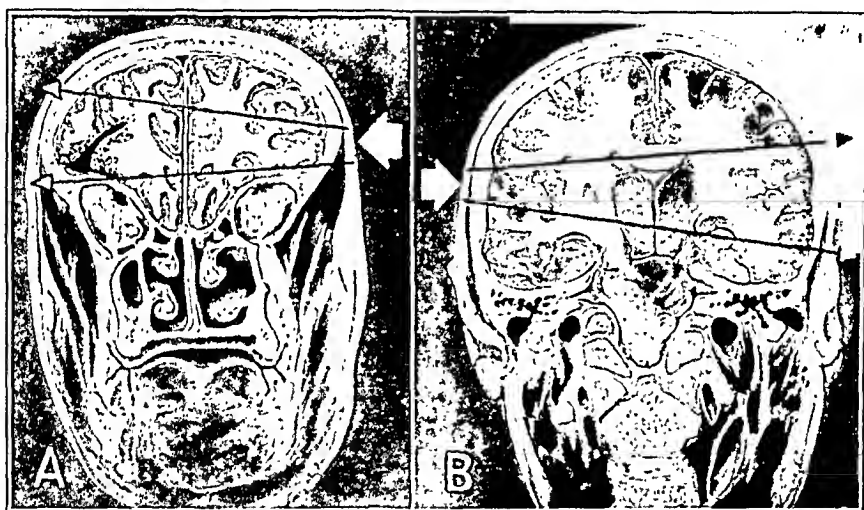


Fig. 6.—Diagrams showing: *A*, contrecoup lateral intrafrontal hemorrhage due to lateral frontal injury; *B*, contrecoup superficial contusion due to lateral temporal injury.

on the same side of the brain. However, if the head is moving in an oblique direction so that the force of the blow is sustained more laterally, the contusions will be largely homolateral if the blow is frontal and largely contralateral if the blow is occipital. The greater the deviation of the point of the application of force is from the midline, the more likely it is that the contusions will be confined entirely to the one side of the brain (fig. 5).

When the head is projected in a lateral direction, the contusions are usually contrecoup; if both coup and contrecoup lesions result, the largest lesions are contrecoup. If the force of injury is sustained in the lateral frontal region, the inferolateral margin of the opposite frontal lobe is apt to be lacerated, often with more or less severe central hemor-

rhage. If the lateral temporoparietal region sustains the impact, the corresponding region of the opposite cerebral hemisphere will be the seat of the lesion (fig. 6). Lateral occipital blows do not produce contusions for anatomic reasons already described.

Still another aspect of the application of force must be considered, that with respect to the direction of the projected head above or below the horizontal plane of the skull. This consideration is most pertinent

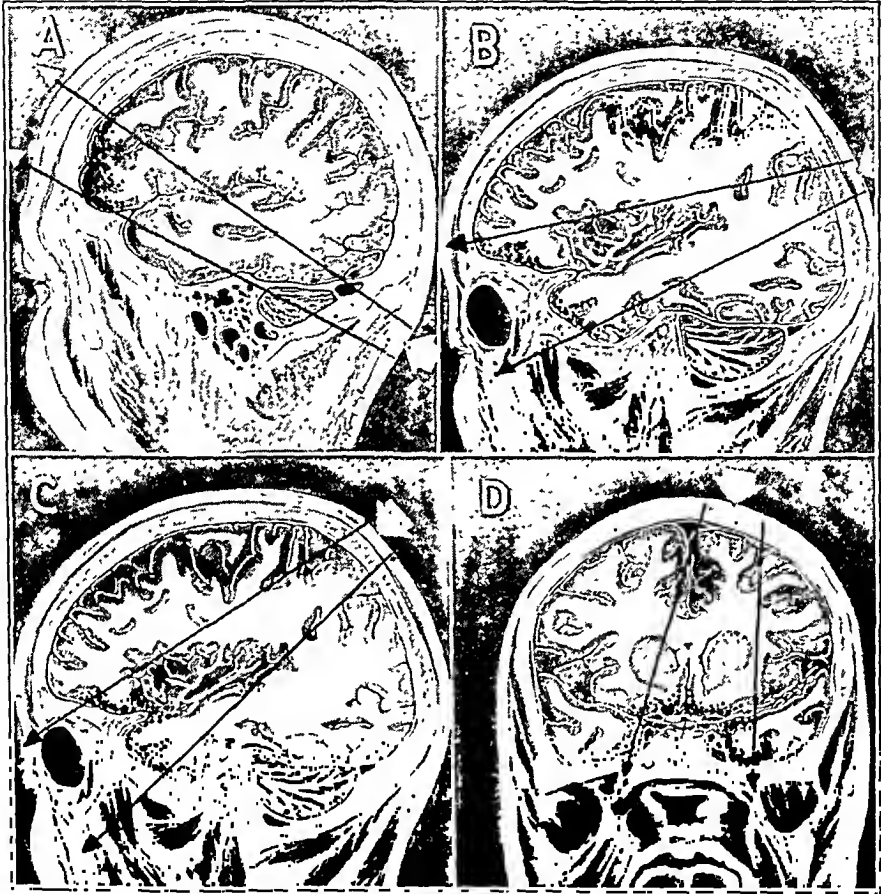


Fig. 7.—Diagrams showing: *A*, contrecoup subfrontal contusion due to median occipital injury; *B*, contrecoup dorsolateral frontal contusion due to low occipital injury; *C*, contrecoup parasylvian (frontotemporal) contusion due to high occipital injury; *D*, contrecoup paramedian (chiasma-splitting) contusion due to vertical injury.

with respect to occipital injuries sustained in falls. If the falling head strikes on the inion, contusions of both subfrontal and anterior temporal regions will usually result. If, by rare chance, the chief force is sustained below the inion, a high frontal polar, or even dorsolateral, contusion will result. In the latter case, the temporal lobes may escape

entirely. On the other hand, if the force is sustained above the inion, the subfrontal and anterior temporal contusions tend to approach each other on either side of the sphenoid ridge. When the brunt of the force is sustained near the vertex, the chiasmal region may be longitudinally split over the sella turcica with resulting homonymous hemianopia if the patient survives his injury (fig. 7).

*Nature of the Lesions Produced.*—As to the nature of the lesions consequent to this mechanism, there are a few points which should be emphasized. Contusions are, of course, the most characteristic and the simplest of coup-contrecoup lesions to evaluate from the standpoint of the mechanism of their production. There are other lesions which con-

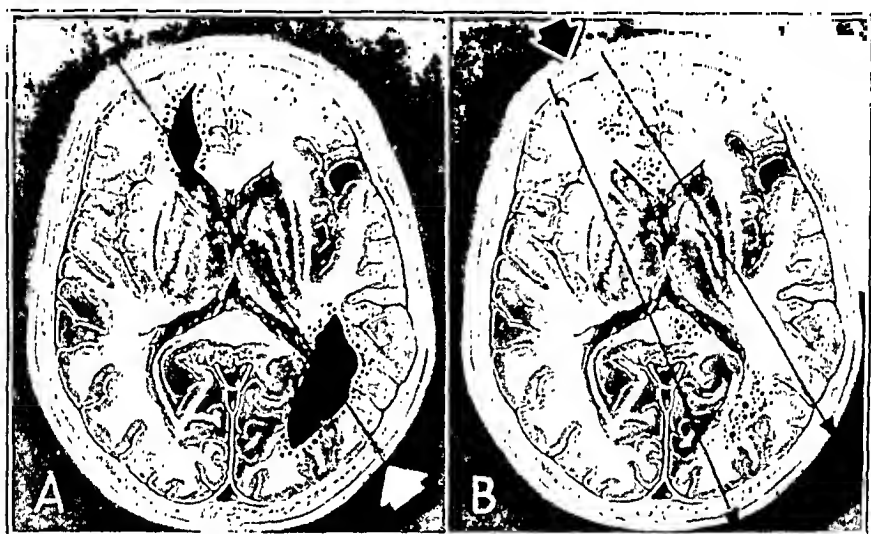


Fig. 8.—Diagrams showing: *A*, intracerebral hemorrhages (temporo-occipital and intrafrontal) along the line of force, illustrating the coup-contrecoup mechanism; *B*, petechial hemorrhages in the cerebral centrum and in the corpus callosum indicative of the coup-contrecoup mechanism.

form, insofar as their location is concerned, with the pattern of the coup-contrecoup mechanism. Outstanding because of the size of the lesion and its clinical importance is traumatic intracerebral hemorrhage. What I term "adjacent" petechial hemorrhages—small perivascular extravasations in the regional centrum of the frontal lobe and, at times, of the parieto-occipital region—are also a product of this mechanism (fig. 8).

In addition, petechial hemorrhages in the genu and the splenium of the corpus callosum and those which appear in the subcortical centrum along the upper and the medial border of the frontal and central regions of the brain probably are also to be accounted for on this basis. In some cases at least, subarachnoid and subdural hemorrhages are also the result

of injury with the head in motion, although a detailed discussion of the anatomic background which makes them possible cannot be gone into in this connection. Suffice it to say, this group of lesions which follow closed injuries, i. e., injuries not dependent on fractures of the skull and sustained with the head in motion, form a pathologic *montage* which is to be clearly distinguished from that consequent to other traumatic mechanisms.

#### CLINICAL OBSERVATIONS

As a result of earlier studies with some of my students in a general survey of craniocerebral injuries, a number of questions arose the answers to which were not immediately evident. For example, it was questioned whether more clinical manifestations of the usually lesser coup injuries of the side of the head could not be elicited if diligently sought for. The question also arose as to why no obvious coup injury to the occipital lobe occurred in cases in which injury was sustained in falls on the occipital region. Or why did no contrecoup injury of the occipital lobe result from frontal injuries by the same mechanism? While it was realized that gross injuries by this mechanism were largely due to the peculiar anatomic relations between the skull and the brain at the particular point, it was difficult to believe that these areas should escape entirely unscathed. It was queried also whether still other evidence in support of the transnervous tissue concept of the coup-contrecoup mechanism might not be forthcoming. It was realized that the answers to these questions were more likely to be found in clinical rather than pathologic observation because the lesions we sought were minor and transitory disturbances of function rather than permanent and gross alterations in structure.

The occurrence of minor and subclinical coup lesions as well as contrecoup lesions in lateral injuries to the head was to be anticipated on the basis of information already at hand. While it was already recognized as a pathologic possibility that with such injuries minor contusions on the side of external injury as well as more severe ones on the opposite side might be found, it was presumed that minor clinical or even subclinical disturbances likewise might occur with less severe injuries. If this proved to be true, then a new avenue of approach to the study of the coup-contrecoup mechanism would be opened up. This proved to be the case in the first of a series of clinical observations:

CASE 1.—A robust left-handed 2 year old son of a physician was struck down by an automobile while playing in the street in front of his home. His projected head struck the pavement in the right frontoparietal region, a small laceration marking the spot. After being lethargic and nauseated for some hours, the boy became mentally clear and responsive. It was then observed that he presented some residual difficulty in motor speech and minor but definite left brachio-

facial hemiparesis. Minor reflex alteration with pathologic toe signs also were found on the right side. This persisted to the extent that the child became right handed.

In this case, it seems clear that a coup injury was sustained in the right lower central area, while the contrecoup injury to the brain was apparently limited to the relatively quiescent minor temporal lobe or so diffused as to result in only minor and transitory reflex changes. This case, however, served to emphasize the fact that even in the presence of minor injuries, coup as well as contrecoup injuries to the brain occur and that evidences of such injuries can often be found if looked for.

In answer to the query as to why no coup injury to the occipital lobe occurs in falls on the back of the head, the following case is cited:

CASE 2.—An adolescent son of a hospital superintendent was playing tennis on a concrete court. After leaping into the air in an effort to return a high lob, he slipped and fell, the right occipital region of his head striking on the cement court. After recovering from a momentary daze, the youth noticed that his vision on the left side was completely obscured (homonymous hemianopia). After resting a few minutes, vision in this field was completely restored, during which interval he was observed by me.

In this case, it is evident that a temporary loss of function of the right visual cortex resulted from some disturbance due to either shock or local circulatory changes consequent to the impact of the occipital region against the concrete. This was obviously a coup lesion sustained with the head in motion for which no anatomic counterpart is found. It seems to bear out the notion that coup effects do occur after falls on the back of the head, even though no grossly visible lesion results from them. These effects are transitory and due to functional rather than structural changes.

As an answer to the question why no contrecoup occipital lobe injuries result from the impact of the moving head in the frontal region, another case may be briefly described as an answer:

CASE 3.—A physician, 33 years of age, consulted me some three weeks after he had been injured. He had been struck by a passing automobile while he was repairing a tire at the roadside. He was thrown some 20 feet (6.1 meters), striking the pavement with the right frontal region. He was unconscious for three days and mentally obtuse for three more. No fractures of the skull were demonstrated by roentgen examination. Aside from headaches, vertigo, ataxia and photophobia, he was conscious of some blurring of vision. Examination disclosed a right upper quadrantic hemianopia to small test objects. This was interpreted as due to a contrecoup lesion of the left occipital lobe.

Here again was found evidence of occipital injury, contrecoup in this case, but more persistent because of the more serious injury; it was subclinical and discovered only by searching for it. It was evidently fading after an interval of three weeks. These 2 cases (2 and 3) seem

to indicate that transitory lesions of the occipital lobe, coup or contrecoup, do occur by this mechanism and according to the laws which govern it. It is also possible that in selected fatal cases, microscopic alterations in the occipital cortex would be discovered if searched for. They would probably be vascular in origin, possibly on an anoxic basis (owing to local transitory disturbances in blood supply incident to *commotio cerebri*).

In addition to these clinical observations which support the essential thesis of the coup-contrecoup injuries of the brain, there was still another which seemed to strengthen the notion that such injuries are produced by transmission of a wave of force through the brain tissue. The essentials of this case are as follows:

CASE 4.—An electrical engineer, aged 56 years, accidentally tripped and fell, striking the back of his head against a concrete retaining wall and sustaining thereby a depressed fracture of the left posterior parietal region. Following restoration to full consciousness after a week, the patient was found to have a bilateral loss of the sense of smell, presumed to be due to bilateral subfrontal contusions. Of particular interest in this connection was the observation that even moderate pressure over the depressed fragment of bone on the left resulted in an acutely severe pain in the right orbit and right temporal region, areas diametrically opposite to the area of depression.

This observation was interpreted as evidence of the transmission of pressure through the intervening nervous tissue with consequent pressure and stretching of the local dura.

#### COMMENT

There are a number of reasons why an understanding of the coup-contrecoup mechanism of craniocerebral injuries is important from a clinical standpoint. In a case of acute injury, a proper evaluation of the mechanism of injury gives the examiner some concept as to the possible nature and location of the lesions of the brain. It helps him to understand the many seeming inconsistencies and complexities which so often appear in such cases.

Perhaps of even greater importance is the evaluation of the patient who has partially recovered from the effects of his injury. Unfortunately, in these cases, it is often difficult or at times impossible to get a complete story of the accident. Nevertheless, the effort spent in such a search is often well repaid. So often the efforts at clinical examination are fruitless because the nature of the problem is not fully appreciated. This is particularly true in the interpretation of encephalograms. Not appreciating that a subfrontal or an anterior temporal contusion may be present, the examiner may be content to see what he considers to be a normal ventricular pattern. The downward enlargement of the anterior horn or horns and the enlargement of the anterior portions of the inferior horns, if visualized at all by the usual views, are likely to be overlooked.

Perhaps of even greater clinical importance today is the possibility of making erroneous evaluations of electroencephalograms. The presence of multiple lesions often gives rise to abnormal waves coming from several locations. Such tracings are apt to be interpreted as due to a diffuse lesion. Or the disturbance in the waves due to clinically quiescent subfrontal and anterior temporal scars may overwhelm or obscure disturbances from some minute lesion provoking occasional post-traumatic convulsions. Such experiences have been met with in my practice recently. It seems important, therefore, that in dealing with patients with post-traumatic difficulties, one should not lose sight of the fundamental principle that the entire problem must be reviewed and that one cannot depend alone on laboratory tests or special examinations, which by their dramatic appeal are apt to elbow their way to the front of the stage. Nothing has thus far been found to entirely replace a knowledge of the evolution of any morbid process and its full evaluation in the light of clinical findings, nor is this likely soon to occur insofar as closed craniocerebral injuries are concerned.

#### SUMMARY AND CONCLUSIONS

It has long been recognized that under certain circumstances, injuries to the brain tissue may occur either on the side of the head sustaining the external injury or on the opposite one. The injury to the brain at the seat of impact has been designated as coup, or direct injury; that of the opposite side of the brain, as the contrecoup or indirect injury.

More recently, it has become evident that this type of closed injury (i. e., without the influence of fractures of the skull) is the result of injury sustained only when the head in motion strikes a stationary or relatively stationary object. The group of lesions thus produced results in a *montage*, which is significant to those familiar with the problem.

Contrary to the belief of some, the lesion is not invariably on the side of the brain opposite to that sustaining the impact. Essentially identical lesions of the subfrontal and anterior temporal regions result from contact of either the frontal region or the occipital region of the moving head, the lesions being coup in the first instance and contrecoup in the second. This fact alone eliminates the original theories proposed to account for the effects of this particular type of injury.

The evident identity of coup and contrecoup lesions already mentioned and the fact that neither gross coup nor contrecoup lesions occur in the occipital region (diffuse contusion due to a somewhat different mechanism excepted) suggest that the anatomic relation of the brain and the portion of the skull proximate to it is essentially responsible for the nature and the distribution of the lesion.

I am of the opinion that contrecoup lesions are produced by a wave of force which is transmitted directly through the nervous tissue and thrusts the cortex of the opposite diameter of the brain against the resisting bony irregularities and contours of the skull. As proof of this theory is offered the chain of lesions through the brain tissue observed in some cases as well as the clinical effect of pressure on the brain in instances of depressed skull fracture.

The most characteristic coup-contrecoup lesion is cortical-subcortical contusion, but gross intracerebral hemorrhages also are to be accounted for on this same basis as well as certain types of petechial hemorrhage and, at least in some cases, subdural and subarachnoid hemorrhage.

It is not possible to make an adequate or complete evaluation of the clinical picture in this group of cases, nor is it possible to interpret correctly the encephalographic or electroencephalographic picture without an understanding of the pathologic results of injury to the brain sustained while the head is in motion.



# TOTAL THYROIDECTOMY FOR CARDIAC DISEASE

## A REEVALUATION

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In a critical evaluation of total thyroidectomy for cardiac disease published in 1937,<sup>1</sup> we based our conclusions on 357 collected and 5 personal cases, the 362 cases including, we believed, practically all of the operations performed up to that time on the indications of cardiac disease. The majority of these cases had been recorded in the literature. The remainder, some of which have apparently not been otherwise reported, we collected by personal correspondence. The largest series (69 cases) was reported from Beth Israel Hospital, New York, where Berlin, on the recommendation of Blumgart, had performed the second such operation in December 1932. The second largest series (42 cases) was reported from the Peter Bent Brigham Hospital, Boston, where Cutler, a month earlier, had performed the first thyroidectomy for heart disease on the recommendation of Levine.

In all, 205 operations had been done for congestive heart failure, with excellent results in 71 cases (34.63 per cent) and satisfactory or partially satisfactory results in 59 (28.7 per cent). One hundred and twenty-eight operations had been done for angina pectoris, with excellent results in 71 cases (55.46 per cent) and satisfactory or partially satisfactory results in 36 (28.12 per cent). In other words, 63.41 per cent of the patients with congestive heart failure and 83.58 per cent of the patients with angina pectoris had been benefited by total thyroidectomy. On the basis of these results, our final conclusion was that the operation was a valuable addition to the therapy of angina pectoris and that some benefit could also be expected from it in treating congestive heart failure, though the results were likely to be less satisfactory.

A distinguished clinician once remarked to one of us that perhaps ten years from the operation's inception neither the Levine-Cutler nor

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Read before the Mississippi Chapter of the American College of Surgeons, Gulfport, Miss., Jan. 31, 1941.

1. Parsons, W. H., and Purks, W. K.: Total Thyroidectomy for Heart Disease, *Ann. Surg.* **105**:722-728 (May) 1937.

the Blumgart-Berlin group would want to claim priority for total thyroidectomy for heart disease, the implication being that many therapeutic measures which at first appear to yield brilliant results are later proved of more doubtful value. We have reluctantly come to the same conclusion. Personal observations since the publication of our first report, an analysis of the recent literature and the results of a questionnaire recently sent to the fifty-five groups and persons who furnished the material for our previous report have caused us materially to alter our previous conclusions as to the value of total thyroidectomy for cardiac disease.

#### THE RATIONALE OF TOTAL THYROIDECTOMY FOR CARDIAC DISEASE

The association of cardiac disorders with thyrotoxicosis and their disappearance after its proper treatment was the basis of Kocher's<sup>2</sup> suggestion in 1902 that toxic thyroid disease be treated by total thyroidectomy. These observations, however, were made from the viewpoint of thyrotoxicosis. It was not until fairly recent years that the reciprocal relation between thyroid activity and cardiac failure began to be observed. In 1925, Christian<sup>3</sup> stated that "a lowered metabolic activity from thyroid deficiency may be a conservative process, a form of cardiac rest that is advantageous to the heart." Soon afterward, the studies of Blumgart and associates<sup>4</sup> and of Burwell and associates<sup>5</sup> demonstrated that the velocity of the blood flow is proportionate to the metabolic demands of the organism and that these demands, in turn, are greatly influenced by thyroid activity.

In myxedema the velocity of the blood flow and the basal metabolic rate are both low. In hyperthyroidism both are increased. In each of these conditions there is no evidence of cardiac decompensation. In congestive heart failure, on the other hand, there is a discrepancy or

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2. Kocher, A.: Ueber Morbus Basedowi, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 9:1-304, 1902.

3. Christian, H. A.: The Heart and Its Management in Myxedema, Rhode Island M. J. 8:109-118 (July) 1925.

4. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: II. The Velocity of Blood Flow in Normal Resting Individuals and a Critique of the Method Used, J. Clin. Investigation 4:15-31 (April) 1927. Blumgart, H. L.; Riseman, J. E. F.; Davis, D., and Berlin, D. D.: Therapeutic Effect of Total Ablation of the Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. 52:165-225 (Aug.) 1933.

5. Burwell, C. S.; Smith, S. C., and Neighbors, DeW.: The Output of the Heart in Thyrotoxicosis, with the Report of a Case of Thyrotoxicosis Combined with Primary Pernicious Anemia, Am. J. M. Sc. 178:157-168 (Aug.) 1929.

disproportionate relation between the metabolic rate and the velocity of the blood flow, the former being normal and the latter being low. It was on the basis of these facts that Blumgart and associates<sup>4</sup> suggested that, since the failing heart cannot be depended on to increase the rate of blood flow, a rational way to overcome the discrepancy between the metabolic rate and the velocity of the blood flow would be to lower the metabolic rate by removing the thyroid gland in toto. In suggesting the same procedure for angina pectoris these authors postulated that since angina is due to the inadequacy of the coronary blood flow in relation to the demands of the heart muscle, removal of the thyroid gland might be expected to reduce the requirements of the heart muscle to such a degree that the coronary blood flow would be adequate.

The physiologic facts are in accord with the hypotheses of Blumgart and associates, but there are nonetheless certain fallacies in their reasoning. The maintenance of the velocity of blood flow, for instance, represents only one factor in the expenditure of cardiac energy. Other factors which also must be taken into consideration include the cardiac output, the blood pressure level and the heart rate. The blood pressure level and the heart rate after thyroidectomy, both at rest and during exercise, do not show significant differences from the preoperative findings. As to the cardiac output, it is difficult to measure, and the findings are often erroneous, especially in patients with congestive heart failure. According to Levine,<sup>6</sup> instead of being increased (and therefore improved) after the operation, it is actually decreased.

Even if the cardiac output could be shown to be improved by the operation, another significant factor must be considered. It is generally agreed that the secretions of the normal thyroid gland are intimately concerned with muscle tone, irritability and contractility and that lack of thyroid secretion affects adversely the amount of work done by skeletal muscle. This is clearly seen in the asthenia of the myxedematous state. Why, then, should not the deficit induced by total thyroidectomy for cardiac disease have a similarly adverse effect on the heart muscle? If the general metabolism and the metabolism of the heart muscle are depressed proportionately, there seems to be no good reason for assuming that the net result would be an improvement in the state of the circulation.

Levine<sup>6</sup> expressed also the opinion that the alteration of the relation between the basal metabolic rate and the velocity of the blood flow which is effected by total thyroidectomy does not offer an adequate rationale for the performance of the operation for congestive heart failure. His actual words, "*If [italics ours] the circulation is improved by this procedure, there must be other factors at work,*" seem to imply that the

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6. Levine, S. A.: *Clinical Heart Disease*, Philadelphia, W. B. Saunders Company, 1936.

operation perhaps does *not* improve the circulation. With this implication and with Levine's further statement that the pathologic physiology of the problem is still unsettled, we are in entire accord. As a matter of fact, we are now of the opinion, as the result of additional observation, that there is no rational basis for assuming that patients with congestive heart failure receive anything but temporary improvement from total thyroidectomy, aside from the improvement inherent in the greatly reduced activity which accompanies the state of myxedema. This temporary improvement is partly psychic and is partly the result of the unusually good preoperative and postoperative care which patients submitted to this operation always receive.

It is true that most patients with congestive heart failure who are submitted to total thyroidectomy have previously failed to respond to medical measures and are likely to have been treated by rest in bed with a minimum of activity for some time before operation. On the other hand, the induction of myxedema by surgical means reduces them to what might be termed subminimal activity, and they benefit accordingly, much as the patient with long-standing cardiac failure may be improved by the administration of a sedative such as morphine. The question then arises whether the degree of improvement to be expected by this mechanism in congestive heart failure compensates for the harmful effects of complete myxedema, which is a rather unhappy state. We no longer believe that it does. We are now of the opinion that total thyroidectomy should not be done on this indication, even in the most carefully selected cases. We have not ourselves employed this operation for congestive heart failure since 1936, and we do not intend thus to employ it in the future.

In a previous communication, one of us (W. K. P.)<sup>7</sup> pointed out that although the theory of Blumgart and associates might possibly explain the results obtained by total thyroidectomy for congestive heart failure, the logic was somewhat strained when applied to angina pectoris. Much more reasonable, in our opinion, is the theory of Levine and associates that the mechanism of relief lies in reflex and humoral alterations, possibly linked with alterations in the adrenal gland.

Angina is a spasmodic disease in which nervous and mental factors play a large part in the production of attacks. It occurs chiefly in persons who have what Houston<sup>8</sup> termed the "spasmogenic aptitude." Coronary disease, although frequently present in association with angina pectoris, is not a major factor in its causation. Coronary disease is frequently

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7. Purks, W. K.: Total Thyroidectomy in the Treatment of Congestive Heart Failure and Angina Pectoris, *New Orleans M. & S. J.* **87**:464-466 (Jan.) 1935.

8. Houston, W. R.: Spasmogenic Aptitude, *M. Clin. North America* **12**:1285-1302 (March) 1929.

observed in the Chinese and Negro races, in which angina is actually rare. Markedly diseased coronary vessels, which sometimes are completely occluded, are often observed at autopsy in persons who never had angina or even any cardiac pain. In other words, although coronary disease is frequently or even usually found in subjects with angina pectoris, an additional factor of spasm is, in our opinion, necessary to the production of attacks. By the same reasoning, we believe that the relief of angina pectoris frequently obtained by total thyroidectomy can be explained by the complete alteration which the operation produces in the patient's personality and in his reactions to various external and internal stimuli. In short, the person with angina pectoris, as the result of the operation, loses his "spasmogenic aptitude," a concept which agrees in principle with the theory of Levine and associates.

Weinstein and associates<sup>9</sup> attempted to explain the fact that patients with angina pectoris in many instances (40 per cent in their own cases) are relieved from pain immediately after total thyroidectomy, long before any change has taken place in the metabolic rate or the velocity of blood flow. They considered it due to the incidental cutting, in the course of the operation, of sympathetic nerve pathways from the heart which pass through tissues adjacent to the thyroid gland, but in our opinion this theory cannot be accepted without reservations. There is considerable divergence of opinion as to whether these nerves, if they are so located, carry afferent impulses from the heart, and the whole question of the relation of the cervical and upper thoracic sympathetic nerves to anginal pain is open to debate. Satisfactory relief of anginal pain by sympathectomy is accomplished only by widespread surgical intervention, and it is difficult to see why one would "accidentally" accomplish in so large a proportion of patients submitted to total thyroidectomy results which painstaking efforts directed along the same line frequently fail to accomplish.

Our own opinion is that the relief of pain which occurs promptly after total thyroidectomy for angina pectoris can more reasonably be explained on the basis of a psychic factor. In the eyes of the patient the operation carries hope of relief from an otherwise hopeless distressing disease, and he therefore approaches it with great optimism. An additional explanation for at least part of the relief of anginal pain after operation is the period of partial narcosis which precedes and follows the procedure.

All of the factors which might be considered in discussing the rationale of total thyroidectomy for cardiac disease have not, of course,

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9. Weinstein, A. A.; Davis, D.; Berlin, D. D., and Blumgart, H. L.: The Mechanism of the Early Relief of Pain in Patients with Angina Pectoris and Congestive Failure After Total Ablation of the Normal Thyroid Gland, *Am. J. M. Sc.* **187**:753-773 (June) 1934.

been mentioned, but in brief summary it might be said that the mechanism of the relief of congestive heart failure and angina pectoris is based on different factors, aside from the excellent preoperative and postoperative care common to both conditions. In congestive heart failure these factors are: (1) early psychic improvement; (2) reduction of physical activity to a subminimal level by the production of the myxedematous state. In angina pectoris they are: (1) a psychic factor, which accounts for the relief frequently observed soon after operation; (2) an alteration of the patient's personality and a loss of the "spasmogenic aptitude," which account for late improvement.

#### SELECTION OF CASES

As with all procedures, the selection of cases for total thyroidectomy is of extreme importance. The trial and error method was necessarily applied when the operation was first introduced, and it is now freely admitted by all proponents of the operation that many mistakes were made. There is now rather general agreement that the sole responsibility for the choice of patients suitable for the operation should rest on the cardiologist and that he should be chiefly responsible also for the pre-operative and postoperative care. It must also be emphasized, as has previously been pointed out, that when this operation is performed, one disease is substituted for another. If the patient with complete myxedema falls later into the hands of physicians either unable or unwilling to supervise his postoperative care, which in fact covers the remaining years of his life, his last state may indeed be worse than his first.

It is generally agreed that no patient with cardiac disease should be subjected to total thyroidectomy until all possible medical measures have been thoroughly tested and have been proved to be of no value. Before this point can be determined, a long period of preoperative observation and adequate medical care is essential. Only in this way can the correct status of the patient be ascertained, since all chronic maladies are subject to natural variations in intensity.

Finally, there is general agreement that all patients submitted to total thyroidectomy should present at least a fair surgical risk. For this reason it is often necessary to delay operation a considerable time, pending improvement in the patient's general condition.

Although we are now of the opinion that the operation is of little or no value in the treatment of congestive heart failure, the criteria by which cases of this kind are selected should nevertheless be mentioned. Levine<sup>6</sup> summed up the whole matter well when he wrote:

. . . In those suffering from extremely advanced lesions, if improvement occurs, it may not last long enough to warrant the operation. On the other hand, the

operation does not seem justified if the disease is only slight or moderate or if the disability is not great. There remains a small group of cardiacs, neither too sick nor too well, who may be suitable for the operation.

Clark, Means and Sprague,<sup>10</sup> whose criteria are essentially in accord with those of Blumgart and his group, established certain contraindications for the operation and regard as suitable for it all intractable subjects who do not fit into them. These contraindications include: inadequate previous medical care; *rapid* decline in spite of medical care; continuing severe decompensation in spite of adequate medical treatment (for example, the development of persistent ascites or hydrothorax); valvular lesions accompanied by high venous pressures; low metabolic rates; chronic pulmonary disease of any type; severe nephritis; malignant hypertension; active rheumatic infection. We agree entirely with these contraindications, and we further feel that they restrict almost to the vanishing point the cases of congestive heart failure in which the operation should be performed, even if benefit could reasonably be expected from it.

Most of the contraindications listed for patients with congestive heart failure apply also to patients with angina pectoris, though naturally they are not so likely to occur in patients with angina. The hypothetical subject in whom the best results might be expected from the operation would be a man between 40 and 60 years of age who has had angina for at least nine months, whose attacks are sufficiently frequent to prevent his following a gainful occupation, who has received adequate medical care but whose attacks have not been controlled by this treatment, who does not have a prohibitive amount of organic damage either in the heart or in the vascular system generally and who presents evidence that he is of the type with a high emotional level, as suggested by the term "spasmogenic aptitude." If the patient uses tobacco, he should not be submitted to operation until he has had a trial period without it.

Not many patients, obviously, will meet these criteria. The majority of persons with angina pectoris can be controlled by appropriate medical measures, including due consideration of the emotional factors, while at the other extreme are patients in whom organic damage may be prohibitive. In the selection of cases clinical judgment is probably the best guide, based on: (1) absence of the contraindications listed; (2) only moderately advanced organic cardiac changes; (3) classification in the group of patients with high emotional levels (expressed or latent); (4) attacks of sufficient severity or frequency to cause complete disability.

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10. Clark, R. J.; Means, J. H., and Sprague, H. H.: Total Thyroidectomy for Heart Disease: Experiences with Twenty-One Patients at the Massachusetts General Hospital, *New England J. Med.* **214**:277-294 (Feb. 13) 1936.

## DEATH AND IMMEDIATE COMPLICATIONS

Since total thyroidectomy for cardiac disease is a formidable procedure, it follows that it should be undertaken only by surgeons thoroughly familiar with the anatomy of the region and with a reasonable experience in operations on the thyroid. The technical procedure varies in certain important details from subtotal resection and must be planned deliberately, step by step. The technic has been well described by Berlin, Cutler and others, and the description need not be repeated at this time, but one or two precautions may profitably be mentioned. The incision must be adequate; this means that the prethyroid muscles must invariably be divided. Great care must be exercised to remove every vestige of thyroid tissue, while at the same time carefully protecting the nerves and parathyroid bodies. Our own preference is for local analgesia or nerve block rather than for any form of general anesthesia.

Since the risk of operation for thyrotoxicosis does not exist in total thyroidectomy done on the indication of heart disease, it is the almost universal and a most desirable practice to perform the operation in one stage, even though the patients do not present in any sense ideal surgical risks. The risks inherent in the operation are accounted for in large measure by their poor condition plus the necessity of invading a danger zone ordinarily avoided in the subtotal operation. On the other hand, our own limited experience, as well as the far more extensive experience of others, shows that total thyroidectomy, even when performed on persons with serious and extensive cardiac disease, does not carry a sufficiently great risk, either of death or of complications, to deter one from applying it when it is indicated.

Comparisons with the mortality rate of the subtotal operation naturally suggest themselves. In the removal of the normal thyroid gland there is no risk of the development of a thyroid crisis, which Lahey<sup>11</sup> stated to be responsible for 40 per cent of the 111 deaths in his personal series of 15,300 subtotal operations. There is also little risk of the development of emboli; these were responsible for 10 per cent of the deaths in Lahey's subtotal operations, but they rarely occur after operation on the thyroid except in the presence of auricular fibrillation, which is not usual in angina pectoris and coronary disease. Heart failure is naturally a possibility in patients with congestive failure, but at that, as we pointed out in our first communication on this subject, we are surprised at the relatively low mortality rate associated with total thyroidectomy for congestive heart failure and the extremely low mortality rate for operations for angina pectoris. In our collected series, we found the mortality rates to be 10.48 per cent in 229 operations performed for congestive heart failure and 3.75 per cent in 133 operations performed for angina pectoris.

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11. Lahey, F. H., in discussion on Parsons and Purks.<sup>1</sup>



In the 362 cases which we collected and studied in our previous communication, it was possible to secure exact data concerning complications in 291. The chief risks are naturally injury to the laryngeal nerve or nerves, and/or removal of the parathyroid bodies with consequent tetany. Myxedema, which is an undesirable consequence of subtotal thyroidectomy, is inevitable and desirable following total ablation of the gland.

Twenty-four of the 291 patients in the collected series (8.2 per cent) suffered injury to the recurrent laryngeal nerve. The injury was always unilateral and was usually transient. Scott,<sup>12</sup> in a recent communication concerning total thyroidectomy in 71 cases of diffuse toxic goiter, had 2 such injuries (2.8 per cent); both were unilateral, and both were permanent.

Tetany occurred in 30 cases (10.3 per cent) of our collected series but fortunately was transitory in all but 1 instance, in which it was apparently the cause of death. Scott reported 3 instances of tetany in his 71 cases (4.2 per cent). One instance was mild; 1 required treatment for a year, and 1 terminated fatally. We have had no instance of either tetany or nerve injury in our personal cases of total thyroidectomy.

#### END RESULTS

There are several reasons for believing that our former conclusions as to the value of total thyroidectomy for cardiac disease were not correct. The first is our personal experience with 4 patients who survived the operation. The 2 patients submitted to the operation for angina pectoris have been followed up since we reported them as doing well in 1937, and they have continued to do well. Neither has been completely rehabilitated, but the results, evaluated conservatively and impartially, may fairly be considered good. The 2 patients with congestive heart failure, however, who also were reported doing well in our first report, have both died, 1 within a year and 1 within three years.

The second reason for our change of opinion is the apparent lack of enthusiasm for the operation at this time on the part of those who formerly recommended and performed it. A review of the literature since 1937 reveals few reported cases. The procedure is evidently being employed in some foreign countries, but the American literature has few articles on the subject, and the initial enthusiasm which colored the early reports is clearly lacking in the papers that are written. Neither Blumgart's nor Levine's group has reported additional cases, and

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12. Scott, A. C., Jr.: Total Thyroidectomy for Diffuse (Exophthalmic) Goitre: Preliminary Report of Seventy-One Cases, *Tr. Am. A. Study Goiter*, 1939, pp. 124-135.

Levine's present skepticism concerning the operation is clear in his recent book on clinical heart disease.<sup>13</sup>

Finally, from a questionnaire recently sent to the fifty-five groups and persons who furnished data for our original collective report, we have received only twenty-five replies, in which only seven reported additional cases. The remaining eighteen replies either express opposition to the procedure or are frankly unenthusiastic about it. For that matter, a similar lack of enthusiasm is apparent in the reports of the seven who have done additional operations. Although it is true that the results of the new cases, when evaluated on the same basis as the cases in the original statistical study, appear to be good, we believe that the failure of cardiologists to recommend and of surgeons to perform additional operations is highly significant.

Our personal experience with the operation since 1937 has been limited to a single patient with angina pectoris, who met the criteria laid down earlier in this paper and in whom the result seems to have been distinctly worth while. We therefore have 3 patients with angina pectoris who survived the operation and in whom the results, observed after sufficiently long periods, have been good.

Good results naturally do not mean that total thyroidectomy is likely to prolong life in patients with angina pectoris. There are no adequate data on which to base such a conclusion. Theoretically, however, it would seem reasonable to expect that life would be prolonged. Any given attack of angina carries a hazard, and the person who suffers two to ten attacks per day is clearly in greater jeopardy than the one who suffers one attack a month or no attacks at all, which is frequently the status of patients who have been submitted to total thyroidectomy. A person with coronary disease, naturally, may suffer coronary occlusion at any time, regardless of whether or not he has anginal seizure.

Since our statistical study in 1937 indicated a considerable probability of relief by total thyroidectomy for both the patient with congestive heart failure and the patient with angina pectoris and since the cases collected in a more recent though less comprehensive questionnaire appear to support the same probability, the question naturally arises as to why we feel that the operation has less merit than the statistical data would

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13. Cutler, E. C., and Hoerr, S. O.: Total Thyroidectomy for Heart Disease: A Five-Year Follow-up Study, *Ann. Surg.* **113**:245-259 (Feb.) 1941. Just after our paper had been completed this excellent article came to our attention. It is based on a careful follow-up study of 57 patients, 16 of whom had survived a five year period of observation. It is of interest that Cutler and Hoerr, on the basis of their extensive experience, concluded that the results of total thyroidectomy for congestive heart failure are disappointing but that the procedure "in a selected group of patients with intractable angina pectoris . . . is a worth while therapeutic measure and is without unwarranted risk."

indicate. We still feel that certain carefully selected patients with angina pectoris might be and actually are benefited by operation, but for several reasons we no longer have the same feeling about the operation for congestive heart failure. The first reason is that if we are to judge by our own experiences, some of the results reported as favorable in our first communication are likely to have proved unfavorable as the period of observation was lengthened. The second reason is, as has already been intimated, that some of the results reported as favorable in our first communication should probably have been discounted because they were obviously colored by the enthusiasm of the men who reported them. The third reason is that if the actual results had been comparable to the statistical evidence of improvement, the literature, instead of a rapidly decreasing number of reported cases, would be likely to show a marked increase, and the persons and groups who supplied the statistical data for our first analysis of the results of total thyroidectomy would show at this time a comparable if not increasing amount of enthusiasm for this mode of treatment.

#### SUMMARY AND CONCLUSIONS

A statistical analysis of 362 collected cases of total thyroidectomy for cardiac disease, including 5 personal cases, was published in 1937. The mortality rate for the operation performed on the indication of angina pectoris was unexpectedly small, and the results were satisfactory or partially satisfactory in more than 80 per cent of the cases. The mortality rate for the operation performed on the indication of congestive cardiac failure was lower than might have been expected, and the results were satisfactory or partially satisfactory in more than 60 per cent of the cases.

An endeavor to continue the analysis has shown that few cases are being reported in the literature, that cardiologists who formerly recommended the procedure and surgeons who formerly carried it out have apparently lost their enthusiasm for it and that results previously reported as favorable have proved to be less favorable or distinctly unfavorable as time has passed.

Our conclusion at this time, based on a recent analysis of the literature, on a questionnaire sent to the persons and clinics supplying the data for the first report and on personal experience is that total thyroidectomy is of negligible value in the treatment of congestive heart failure, as might be expected in the complete absence of any theory which can reasonably explain why improvement should occur. On the other hand, there is reason to believe that certain carefully selected patients with angina pectoris may be and actually are benefited by the operation, and it should be considered in cases in which medical measures have proved ineffective.

# PSEUDOMYXOMA PERITONAEI IN A MAN

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Among the strange pathologic curiosities are mucocoele of the appendix and its even rarer companion, pseudomyxoma peritonaei. We are convinced from conversations with several surgeons that these conditions are more frequently encountered than recognized. When one considers the high percentage of appendixes in which the lining mucosal cells continue to secrete in the presence of a lumen obliterated at some point, one marvels that this combination of circumstances does not result more often in mucous distention of the organ or, as Féré<sup>1</sup> in 1876 named the condition, mucocoele of the appendix.

Rokitansky,<sup>2</sup> in 1842, and Virchow,<sup>3</sup> in 1863, were the first to discover mucocoele of the appendix and considered it a colloid degeneration of carcinoma. Werth,<sup>4</sup> in 1884, first recognized and named the condition known as pseudomyxoma peritonaei. Formerly considered to be exclusively of ovarian origin, it was Fraenkel,<sup>5</sup> in 1901, who, observing pseudomyxoma peritonaei in a male patient, realized that it could arise from a mucocoele of the appendix. In 43,000 appendectomies at the Mayo Clinic reviewed by Woodruff and McDonald,<sup>6</sup> 146 mucocoeles of the appendix were encountered. Castle's<sup>7</sup> figures from 13,158 postmortem examinations place the occurrence at 0.2 per cent of all cases of disease of the appendix.

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From the Department of Pathology and the Surgical A Service, Hospital of the Protestant Episcopal Church.

1. Féré: Mucocèle de l'appendice iléo-cæcal, *Progrès méd.* **5**:73, 1876.

2. Rokitansky, C., cited by Weaver.<sup>8</sup>

3. Virchow, R.: *Virchows Arch. f. path. Anat.* **27**:250, 1863; cited by Weaver.<sup>8</sup>

4. Werth: *Klinische und anatomische Untersuchungen zur Lehre von der Bauchgeschwülsten und der Laparotomie*, *Arch. f. Gynaek.* **24**:100, 1884.

5. Fraenkel, E.: *Ueber das sogenannte Pseudomyxoma peritonei*, München. med. Wchnschr. **48**:965, 1901.

6. Woodruff, R., and McDonald, J.: *Benign and Malignant Cystic Tumors of the Appendix*, *Surg., Gynec. & Obst.* **70**:750, 1940.

7. Castle, O. L.: *Cystic Dilatation of the Vermiform Appendix*, *Ann. Surg.* **61**:582, 1915.

Weaver<sup>8</sup> mentioned 256 reported cases of mucocoele of the appendix up to 1937, in 49 of which pseudomyxoma peritonaei resulted. Of these cases, the patients were male in only 14. Since 1937, when Weaver,<sup>8</sup> Morgan<sup>9</sup> and Voigt<sup>10</sup> independently reported cases of pseudomyxoma peritonaei of appendical origin, no cases have been reported in the English literature. We became interested in the subject when we recently encountered a case of mucocoele of the appendix with pseudomyxoma peritonaei in a male patient. In this case, the clinical diagnosis, the pathologic picture and the surgical procedure were carefully considered. We believe that this is the fifteenth case of its kind ever published.

#### CAUSATION

Although the causation of mucocoele of the appendix and pseudomyxoma peritonaei is still largely a matter of conjecture, most authors are agreed on several feasible theories. Between the age groups of 25 to 60, when the appendix is involuting, or at any time following healing from recurrent exacerbations of acute appendicitis, the lumen, usually at the proximal end, may become obliterated. Continued secretion of mucus results in distention of either a part or the whole of the appendix. Most authors have expressed the opinion that the mucosa must be sterile in order to form a mucocoele. Lifvendahl and Ries,<sup>11</sup> however, suggested that residual low grade inflammation may stimulate the mucous glands to secrete. Grodinsky and Rubnitz<sup>12</sup> concurred with this idea from their experimental work with rabbits in which they produced mucocoeles in appendixes which were flushed clean but not sterile before ligation.

Because of increased intraluminal pressure, the mucosa may herniate through the weakened muscle wall as diverticula, which may eventually rupture. When the exudate is deposited in the peritoneal cavity, loose lining cells of the appendix are thrown out; the materials disseminate more or less widely, depending on their volume and the reaction of the peritoneum. Having discharged its content, the appendix may then collapse and the perforation heal. This sequence of events may recur repeatedly over a period of years. Our experience adds nothing to what is recorded in the literature to enlighten the mystery of a time interval relation between the formation of a mucocoele of the appendix and the

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8. Weaver, C. H.: Mucocoele of the Appendix with Pseudomucinous Degeneration, *Am. J. Surg.* **36**:523, 1937.

9. Morgan, J. O.: Mucocoele of the Appendix, *J. M. A. Alabama* **7**:14, 1937.

10. Voigt, W. W.: Pseudomyxoma Peritonei and Its Ultimate Development, *Illinois M. J.* **71**:172, 1937.

11. Lifvendahl, R. A., and Ries, E.: Open Communication Between Mucocoele and Cecum, *Am. J. Surg.* **17**:270, 1932.

12. Grodinsky, M., and Rubnitz, A. S.: Mucocoele of the Appendix and Pseudomyxoma Peritonei, *Surg., Gynec. & Obst.* **73**:345, 1941.

appearance of a recognizable pseudomyxoma peritonaei. Perhaps much depends on the ability of the implanted cells to secrete.

Being a foreign body, the thick mucoid material from the appendix sets up chronic serositis when it comes in contact with the peritoneum. As the mucus forms in excess of absorption, fibrin from the serum secreted by the serosa surrounds droplets of the material and divides them into individual ball-like units admixed with columnar epithelial cells. Grodinsky and Rubnitz<sup>12</sup> showed that a ground filtrate of pseudomyxoma peritonaei from 1 rabbit injected into the peritoneal cavity of other rabbits was incapable of forming pseudomyxoma peritonaei. The reverse was true when the mucoid exudate containing intact epithelial cells was implanted. On the other hand, as far back as 1910, Trotter<sup>12a</sup> suggested that the mucoid exudate from the appendix stimulated a metaplasia of the endothelial cells of the peritoneum into a tall columnar form with the ability to secrete. Although this theory is not popular, it is unlikely that it can be disproved on scientific grounds with regard to the human being. The possibility that the implants are the result of a combination of these factors, in at least a few cases, must be considered.

#### PATHOLOGIC APPEARANCE

The gross pathologic appearance of pseudomyxoma peritonaei may be readily recognized, although the extent of peritoneal involvement and the degree of distortion of the appendix vary considerably in the cases reviewed. It is rare for a case in which the condition is minimal or in an early stage to be described, since only when the condition is well advanced does it cause symptoms. The mucocoele may vary from 3 cm. in length to the size of a football. Regardless of the size of the mucocoele of the appendix, its rupture is necessary to form pseudomyxoma peritonaei. This is emphasized by the fact that some of the largest mucocoeles have been unassociated with pseudomyxoma peritonaei. A feature often encountered by surgeons is the occurrence of one or more completely walled-off, mucoid-filled cysts varying greatly in size. These cysts may be close to the appendix or some distance from it. Attempted removal of them has not infrequently resulted in rupture of a thin-walled portion. Morgan<sup>9</sup> reported a case of an inoperable single cyst filling the entire abdomen, from which a total of 21 liters was removed. Later, it was demonstrated that this cyst was separate from the appendix. In our case, no cysts other than the mucocoele existed, although advanced pseudomyxoma peritonaei was evident.

The wall of the appendix undergoes some fibrous thickening as if in response to chronic inflammation. Classically, the lumen at the proximal

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12a. Trotter, W.: Peritoneal Pseudo-Myxoma Originating from the Vermiform Appendix, Brit. M. J. 1:687, 1910.

end is closed. Dodge,<sup>13</sup> however, mentioned 5 cases in which the lumen was patent. It is conceivable that in these cases the pressure of the accumulated mucus could have forced itself through a preexisting channel into the cecum. This seems likely, for in none of Dodge's cases did a mucocele rupture into the peritoneum to form pseudomyxoma peritonaei.

Histologic sections of mucocele of the appendix show pictures which vary from areas of normal mucosa to a thickened fibromuscular wall lined by hyperplastic and hypertrophied cylindric epithelial cells, some of which may be actively secreting. If the appendix is greatly distended, many areas may be devoid of mucosa from pressure atrophy. Some round cell infiltration is often present.

Grossly, the tenacious matter of pseudomyxoma peritonaei is found free and implanted on the peritoneal surfaces. In most cases the exudate is confined to a small area of the right lower quadrant of the abdomen. In a few of the reported cases, the process was more widely disseminated, involving, as it did in our case, the viscera of all quadrants of the abdomen, the mesentery of the bowel and the peritoneum. Regardless of the extent of the lesion, the exudate (fig. 1) grossly consists of golden yellow gelatinous mucoid material, referred to commonly as "frog spawn" or "fish eggs," admixed with a cloudy serous fluid.

Typically, in sections of the frog spawn exudate (fig. 2), one sees fibrin and abundant eosin-staining mucinous material through which are occasionally scattered long chains of tall columnar epithelial cells tending to form large cysts.

Pseudomyxoma peritonaei has not been well discussed from the histologic point of view, and in many cases, pseudomyxoma peritonaei originating from mucocele of the appendix has been considered to be malignant on clinical grounds, but there has been no histologic description of the implants in these cases. Having excellent operative and post-mortem specimens, we have endeavored to determine: (1) the similarity, if any, to pseudomyxoma peritonaei derived from cystadenoma of the ovary; (2) whether the process was of neoplastic or inflammatory nature, and (3) what, if any, contributions it makes to the patient's death. In our case, evidence was presented of suggestive malignant degeneration occurring in pseudomyxoma peritonaei along with benign mucocele of the appendix.

Not enough investigative work has been done to compare properly the features of pseudomyxoma peritonaei of ovarian origin with those of the process of appendical origin. In the most recent work by von Nányay<sup>14</sup> in a German paper, mucocele is considered the source

13. Dodge, G. E.: Cystic Dilatation of the Appendix, *Ann. Surg.* **63**:334, 1916.

14. von Nányay: Die Rolle der Wurmfortsatzzysten in der Entstehung der Pseudomyxoma Peritonei, *Beitr. z. klin. Chir.* **171**:74, 1940.

of pseudomyxoma peritonaei, and tumors of the ovary are mentioned only in passing as the cause usually attributed. Pseudomyxoma peritonaei is usually of ovarian origin, but some authorities<sup>15</sup> have expressed the opinion that in many cases a mucocele of the appendix may have been overlooked. Voigt<sup>10</sup> recalled that in cases of pseudomyxoma peritonaei, mucocele of the appendix and cystadenoma of the ovary often occur simultaneously. Reinike<sup>15a</sup> observed that in female patients with pseudomyxoma peritonaei, if both the appendix and the ovarian tumor were not removed, recurrences of pseudomyxoma peritonaei were more rapid. Based on work by Masson and Hamrick<sup>16</sup> on ovarian pseudomyxoma peritonaei and on opinions by several other authors concerning the appendical origin of the condition, the following comparison is offered:

Pseudomyxoma Peritonaei Originating in Mucocele of the Appendix	Pseudomyxoma Peritonaei Originating in Ovarian Cystadenoma
Origin: Mechanical obstruction of the lumen and rupture of a muco- cele	Neoplasm: rupture of the cyst
Clinical course: More benign	More malignant
Prognosis: Better	Worse
Histologic nature of implants: Malignant in 38 per cent; not so cellular; chains of single cells	Malignant in 43 per cent; more cellular; alveolar and papillomatous tendencies present in many
Gross characteristics: Single mucocele	Bilateral ovarian tumors in 50 per cent; bilateral involvement in 73 per cent of the cases in which the process was malignant
Reaction of exudate: Acid	Alkaline

A reasonable search of the literature has not revealed to us whether pseudomyxoma peritonaei can occur in the absence of a ruptured ovarian cystadenoma. It seems that this might be possible, especially in cases of ovarian cystadenocarcinoma, in which cells penetrating as far as the serosa of the cyst could undergo cell division and secretion with the formation of pseudomyxoma peritonaei. Ewing<sup>17</sup> pointed out that ovarian cystadenocarcinoma spreads mainly by peritoneal implants but that it may extend to lymph nodes, such as the retroperitoneal and the inguinal, and, rarely, to distant organs. Lymphatic invasion does not occur with pseudomyxoma peritonaei from mucocele of the appendix.

15. (a) Reinike, W.: Problem of Pseudomyxoma of the Peritoneum, *Ginek.* 8:347, 1937. (b) Morgan.<sup>9</sup> (c) Voigt.<sup>10</sup>

16. Masson, J. C., and Hamrick, R. O.: Pseudomyxoma Peritonei of Ovarian Origin: Analysis of Thirty Cases, *S. Clin. North America* 10:61, 1930.

17. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940.



When ovarian tumors produce pseudomyxoma peritonaei, the degree of malignancy varies considerably. Histologically, the implants from ovarian cystadenoma are generally more malignant than are those from mucocoele of the appendix. Novak<sup>18</sup> pointed out that even in cases of frankly benign ovarian papillary serous cystadenoma, there can be no certainty as to a benign clinical course.

In none of the articles on pseudomyxoma peritonaei with which we are familiar is colloid carcinoma of the gastrointestinal tract mentioned in the differential diagnosis. Because of the gross appearance of pseudomyxoma peritonaei and its colloid nature, we feel that this condition must have entered the minds of many who encountered it as it did ours. We have been unable to find a single instance of pseudomyxoma peritonaei which has had its origin in colloid carcinoma of the gastrointestinal tract. Little has been written concerning the metastatic peritoneal implants of colloid carcinoma. Two cases reported in the *New England Journal of Medicine*<sup>19</sup> and a section in MacCallum's textbook<sup>20</sup> reveal certain characteristics which distinguish colloid carcinoma from pseudomyxoma peritonaei, namely: (1) definite clinical evidence of a primary lesion in the intestinal tract; (2) metastatic implants less colloid than the primary lesion; (3) absence of any large quantity of freely floating frog spawn exudate; (4) grossly, more invasion and the presence of visceral metastasis; (5) histologic evidence of malignancy.

#### CLINICAL PICTURE

There is no characteristic clinical syndrome associated with mucocoele of the appendix, and indeed the condition is rarely diagnosed preoperatively. Among all the cases reviewed by Dodge<sup>22</sup> and Morgan<sup>9</sup> there was only 1 case of mucocoele of the appendix correctly diagnosed preoperatively or before autopsy. Since then, Ruddock<sup>21</sup> has listed mucocoele of the appendix as a preoperative diagnosis made by peritoneoscopy. We believe ours to be the third correct preoperative diagnosis, and it, too, was made by peritoneoscopy. In this case, the instrument corrected a previous clinical impression of metastasis of carcinoma of the bowel and led to an elective appendectomy.

18. Novak, E.: *Gynecological and Obstetrical Pathology*, Philadelphia, W. B. Saunders Company, 1940.

19. Colloid Carcinoma of Stomach (Primary) with Hepatic and Peritoneal Metastases, Cabot Case 23321, *New England J. Med.* **217**:270, 1937. Colloid Carcinoma of Stomach with Metastases to Mesenteric and Cervical Lymph Nodes and Bone Marrow, Cabot Case 24411, *ibid.* **219**:577, 1938.

20. MacCallum, W. G.: *Textbook of Pathology*, ed. 7, Philadelphia, W. B. Saunders Company, 1940.

21. Ruddock, J. C., in Davis, C. H.: *Gynecology and Obstetrics*, Hagerstown, Md., W. F. Prior Company, Inc., 1935, vol. 3, chap. 16, p. 3.

Of the cases of mucocele of the appendix in which operation was done, in about half there was a history of pain, discomfort or other vague symptoms referable to the right lower quadrant of the abdomen. In the other half, no symptoms were present. Attacks years previously of acute appendicitis for which no operation was performed characterize the history in many cases. In those resulting in pseudomyxoma peritonaei, painless abdominal swelling, varying in duration from six weeks to three years, loss of weight, exhaustion and anorexia make up the usual picture, although abdominal swelling is the only constant finding. Even this is absent except in cases in which the condition is advanced. Signs of gradual intestinal obstruction frequently occur as a terminal event in cases in which the condition is advanced. Mayo<sup>22</sup> suggested that mucocele of the appendix should be considered whenever there is distress and a palpable mass in the right lower quadrant of the abdomen, especially in a male patient. Mucocele of the appendix has been observed in subjects from 4 to 72 years of age, the average age being 41 years. It is strange that although mucocele of the appendix is more frequent in male patients, it produces pseudomyxoma peritonaei four times as often in females.

#### PROGNOSIS

The prognosis of uncomplicated mucocele of the appendix is good. From the Mayo Clinic, the younger Charles Mayo<sup>22</sup> reported 70 cases in which simple appendectomy was done for mucocele of the appendix without an operative death. Complete spontaneous regressions of pseudomyxoma peritonaei after appendectomy have been reported. Clinically, most cases are fatal in two to three years after appendectomy in spite of the comfort afforded by courses of postoperative irradiation.

The complications from simple mucocele of the appendix suggested by Jones and Carmody<sup>23</sup> are: (1) intussusception; (2) invagination; (3) volvulus; (4) intestinal obstruction; (5) occurrence in a hernial sac; (6) gangrene; (7) rupture of vessels. Carcinoma and pseudomyxoma peritonaei obviously should be added to this group. Jefferies<sup>24</sup> stated that of all the cases of pseudomyxoma peritonaei fully reported to 1932, in about 62 per cent the process was benign and in 38 per cent, it was malignant. Woodruff and McDonald<sup>6</sup> expressed the belief that pseudomyxoma peritonaei of appendical origin is derived from low grade cystadenocarcinoma of the mucocele and not from benign mucocele. In

22. Mayo, C.: Mucocele of Appendix with Case Report, *Minnesota Med.* **15**: 254, 1932.

23. Jones, T., and Carmody, M.: Mucocele of Appendix, *Am. J. Surg.* **31**: 511, 1936.

24. Jefferies, J.: Pseudomyxoma Peritonei, *Ann. Surg.* **96**:215, 1932.

10 cases included in their review of 146 cases, the mucocoele of the appendix was of a low grade of malignancy, and none of the total group produced pseudomyxoma peritonaei. That a mucocoele is necessarily malignant seems unlikely in view of the experimental work by Grodinsky and Rubnitz, who produced benign mucocoele of the appendix and pseudomyxoma peritonaei in rabbits. The findings in our case substantiate those of others<sup>25</sup> in that no malignancy was observed in the sections made from the mucocoele of the appendix in a case in which widespread pseudomyxoma peritonaei was present.

From a histologic standpoint, in most cases pseudomyxoma peritonaei of appendical origin is benign in that actual carcinomatous cellular characteristics have not been reported. However, it should be emphasized that the complications leading to death occur regardless of cellular detail, inasmuch as they are of a mechanical, rather than an invasive, nature. From the clinical and the autopsy study in our case, we are able to suggest several complications of pseudomyxoma peritonaei, any one or a combination of several of which may cause the patient's death: (1) inability of the peritoneum to withstand the slightest infection (this has already been emphasized by Voigt<sup>10</sup>); (2) gangrene of the appendical stump with perforation after appendectomy; (3) intestinal obstruction from incarceration due to compression of the peritoneal exudate around the curling loops of the small bowel; (4) gradual small bowel infarction from impaired portal venous return caused by compression of the exudate on the mesenteric veins; (5) malignant degeneration.

#### REPORT OF A CASE

A 62 year old white man was admitted to the hospital on Feb. 22, 1941, with a history of five weeks' duration of moderately severe burning pain in the upper part of the abdomen radiating to the left flank, accompanied by progressive abdominal enlargement, constipation and moderate anorexia. He had lost 20 pounds (9.1 Kg.) since the summer of 1940. The past medical history was negative.

Physical examination revealed a fairly well developed but undernourished man with signs of pulmonary emphysema, bilateral elevation of the diaphragm and marked abdominal ascites. Rectal examination revealed a normal prostate. About 4 cm. within the rectum, the examining finger made contact with a uniformly smooth constriction of the lumen which did not have the irregularity and the resistance of carcinoma. A sigmoidoscope could not be passed beyond the first turn of the rectum owing to the resistant constriction. The mucosa appeared normal. No intrinsic lesion was seen.

By roentgen examination, no organic lesion in the colon was demonstrated. It was noted that the junction of the sigmoid and the descending colon did not have a large caliber and was not freely movable. The examination was not satisfactory owing to ascites.

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25. Weaver.<sup>8</sup> Voigt.<sup>10</sup>

Laboratory examinations were made with the following results: The urine was normal. The hemoglobin content of the blood was 74 per cent. The red blood cell count was 3,880,000. The white blood cell count was 9,200, with 72 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 4 per cent monocytes, 3 per cent eosinophils, 2 per cent basophils and 59 filamented forms and 13 non-filamented forms. The Wassermann and Kahn tests were negative.

As had been the experience of others, there was no clue in this case to aid in making a correct diagnosis. Because lesions of the rectum are rarely demonstrated by roentgen examination and because of the atypical rectal and proctoscopic findings, a tentative diagnosis of carcinoma of the rectum with generalized carcinomatosis was made. With the idea of relieving distention by paracentesis and confirming the diagnosis, the patient was referred to one of us for peritoneoscopy on March 4.



Fig. 1.—Photograph of a culture of pseudomyxoma peritonaei in a Petri dish showing clusters of sharply circumscribed gelatinous material resembling fish eggs. Seven liters of this material was withdrawn through the peritoneoscopy sheath.

*Peritonoscopy.*—Thick gelatinous blood-tinged fluid (7,000 cc.) admixed with frog spawn-like material was withdrawn through the sheath (fig. 1). The exudate was too thick to have been removed through a tube less than 12 mm. in diameter. Inspection with the peritoneoscope was most satisfactory and revealed multitudinous masses of honey-colored translucent gelatinous material adherent to the parietal peritoneum over the stomach and the omentum. There were a few nodules on the liver, but the remainder of this organ appeared normal. The lesions did not appear firmly attached and implanted as in carcinoma. They gave the impression that a stroke of the finger would easily brush them away. Inspection of the lower quadrants of the abdomen revealed myxomatous implants in every quarter, and with the patient in the Trendelenburg position, there appeared to be a large mass

of the material between the bladder and the rectum. A diagnosis of pseudomyxoma peritonaei was made with the inference that mucocele of the appendix was the most likely source.

*Histologic Examination.*—The exudate (fig. 2) consisted of pinkish mucinous material admixed with fibrin through which were scattered long chains of well differentiated tall columnar epithelial cells tending to form large cysts or acini.



Fig. 2.—Photomicrograph of peritoneal exudate of pseudomyxoma peritonaei. Note the chain of well differentiated cylindric cells admixed with fibrin and mucinous exudate. A few mononuclear cells and fibroblasts are present. (Hematoxylin-eosin stain;  $\times 450$ .)

Leukocytes and red blood cells were irregularly scattered. The material gave the chemical reactions for pseudomucin.

For the next twenty-seven days, the patient felt much better, the fluid did not reaccumulate, and he went about his daily work at home free from pain.

*Operation.*—On March 31, appendectomy was performed with the patient under spinal anesthesia. Through a right paramedian hypogastric incision the peritoneal cavity was entered, and a condition of pseudomyxoma peritonaei was encountered similar to that observed by peritoneoscopy. A large amount of myxomatous material was manually delivered, and extensive infiltration of the omentum was particularly noted. An attempt was made to isolate the appendix, and in the exploration a cystic mass was felt in the pelvis just beyond the pelvic brim on the right side. During delivery, the mass ruptured through a thin-walled portion, evacuating 65 Gm. of clear thick mucinous material. The mass was dissected farther up and was found to be continuous with, or to actually be, the appendix, having its origin at the ileocecal junction. The appendix was removed, and the stump was doubly

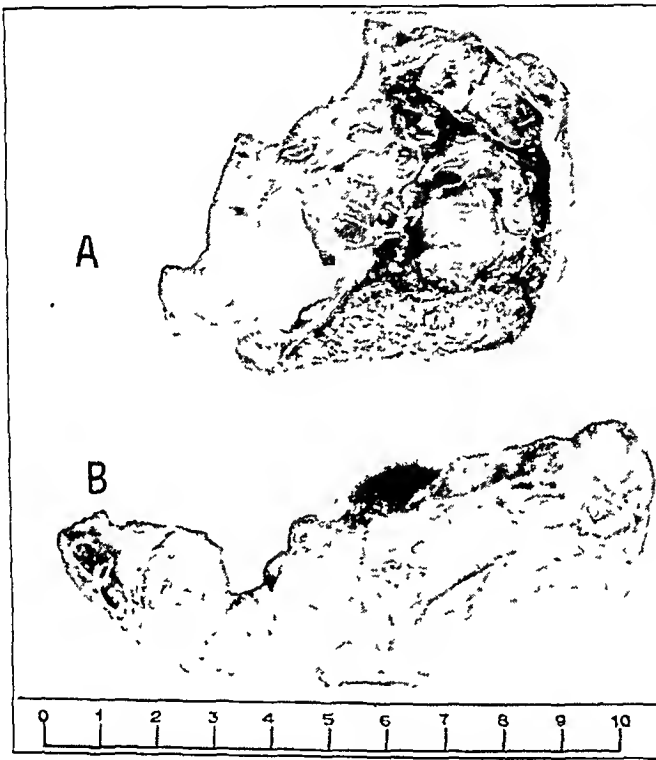


Fig. 3.—*A*, photograph of a portion of the spleen showing thickened capsule and pulp invaded by thick-walled multiloculated cysts filled with golden yellow gelatinous material. *B*, photograph of a mucocoele of the appendix (less than actual size owing to mounting). To the left is the thick-walled proximal end with the obliterated lumen; to the right is the thin-walled distended portion which contained 65 Gm. of thick gelatinous mucoïd material. (Ruler shows centimeters.)

ligated with no. 1 chromic catgut without being buried. The wound was closed in layers without drainage.

*Pathologic Report.*—The specimen (fig. 3) consisted of a membranous sac, 10 cm. long, 4.5 cm. in diameter at the distal end and 2.5 cm. at the proximal end and weighing 33 Gm. The serosa was pinkish and smooth except where adhesions had been torn away or where implants of yellowish mucoïd material were attached. The wall of the distal end, which had ruptured, was paper thin. The inside of the sac was smooth except for some trabeculation. The proximal end

was solid, devoid of a lumen and composed of compressed colloid-like islands. It contained the material already described as rupturing during operation. In addition, a biopsy of omentum containing gelatinous colloid material was made.

*Microscopic Examination.*—Sections of the appendix (fig. 4) cut just distal to the obliterated proximal end revealed recognizable muscularis, but without the crypts of Lieberkühn or the solitary lymphoid follicles. The thickened wall consisted of muscle and well organized hyalinized fibrous tissue. Lining part of the



Fig. 4.—Photomicrograph of a section from the wall of a mucocoele of the appendix showing the secreting epithelial cells, the absence of submucosa and the fibrous muscularis. Some of the pseudomyxoma peritonaei is on the outside of the wall (right). Most sections of the appendix did not reveal any mucosa. (Hematoxylin-eosin stain;  $\times 120$ .)

lumen was a single layer of well differentiated epithelial cells varying in form from low cuboid to tall columnar. The tall columnar cells could be clearly seen to be secreting. The contents were composed of a bluish pink-staining homogeneous mucoid-like material. Except for a few isolated columnar cells, the lining of the rest of the appendix was devoid of mucosa.

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The sections used in biopsy of the omentum were similar to the peritoneal exudate removed three weeks previously, except that, in addition, a few goblet cells were present, and there was evidence of secretion. The cells were well differentiated, and there was no appearance of malignancy. Surrounding these cells were broad bands of collagenous and fibrous connective tissue. Some mononuclear cell infiltration and fibrosis confirmed the chronic serositis exerted by the exudate.

*Postoperative Course.*—For three days after operation, the patient's course was uneventful. After this, signs of gradually progressive chronic intestinal obstruction



Fig. 5.—Photograph showing: in the lower half, the omentum, which weighed 1,300 Gm.; in the upper half, a loop of large bowel turned in the midportion to display smooth mucosa and myxomatous involvement of the serosa; in the upper left, a mucocoele of the appendix. (Ruler shows inches.)

without pain developed. The temperature oscillated between 98 and 101.5 F. The patient died twelve days after operation.

*Autopsy.*—Discussion of the autopsy is limited to the abdomen because the remaining parts were noncontributory to the case or the cause of death.

The abdomen was tense, distended and flat to percussion. On entrance into the peritoneal cavity, a strange pathologic curiosity was encountered. The cavity contained 2,000 cc. sanguineous fluid in which floated flecks of pseudomyxomatous material. The entire peritoneum and the large apron of omentum (fig. 5) obscuring



the viscera were covered by a dense mass of closely knit myxomatous nodules varying in size from 2 mm. to cystic areas 2 cm. in diameter, which contained thick gelatinous clear yellowish material. The omentum weighed 1,300 Gm. and measured 35 by 15 by 4 cm. It was boardlike in consistency and adherent to the underlying viscera.

With the omentum freed, the large and the small bowel were seen to be covered with this same myxomatous process as well as a whitish foul-smelling fibrinopurulent exudate; obviously, generalized acute suppurative peritonitis was present. Handling the viscera resulted in the expulsion of flatus through the peritoneal fluid of the lower right quadrant of the abdomen. The widespread heavy myxomatous exudate so securely encased the viscera that removal of the intestinal tract was extremely difficult owing to the confusion of anatomic landmarks. Segments of the small intestine were kinked by the plastic exudate. It is difficult to understand how bowel contents traversed these loops, yet the small intestinal contents were fluid throughout. The mesentery of the small intestine and the sigmoid was greatly thickened by a coating of the peritoneal exudate. The tone of the small and the large bowel was poor; the color, dark. The cecum was particularly soft, thin walled and dark. A perforation was present at the site of the appendical stump, thus accounting for the flatus and generalized peritonitis. No suture material was seen, and there was no gross gangrene or necrosis about the perforation. The mucosa of the entire gastrointestinal tract was essentially normal (fig. 5), aside from the suggestive degeneration and darkening continuous with this appearance on the serosa of the small intestine. At no point had the myxomatous implants invaded the mucosa.

The liver and the gallbladder were normal aside from the frog spawn implants limited to their external surface. The spleen (fig. 3) weighed 200 Gm. Interposed between the diaphragm and the spleen, connecting the two, were multiloculated thick fibrous-walled cysts filled with yellowish gelatinous material. The splenic capsule was thickened, and the mushy pulp had been invaded in numerous areas by gelatinous material similar in all respects to the abdominal exudate.

The adrenals, the kidneys, the bladder and the pancreas were essentially normal.

*Microscopic Examination.*—Sections of the stomach and the small bowel revealed noninvasive myxomatous implants and purulent peritonitis confined entirely to the serosa. The large intestine (fig. 6), being more inadequately protected by the omentum, revealed even greater acute peritonitis. The chronicity of pseudomyxoma peritonei was typified in sections of the large bowel. Here, confined to the serosa, were dense fibrous strands and myxomatous material well supplied by small blood vessels. The clusters of acini were actively secreting. Some neoplastic tendency was present in a few sections of the large intestine (fig. 7). This was characterized by large acini formed of tall deep eosin-staining actively secreting cells with large pale nuclei. Such hyperplasia of cells occurred that solid clusters were formed, and in some areas nothing but nuclei and pale vacuoles were present. Atypical mitosis was observed, as was also invasion beyond a basement membrane. The size and the activity of these cells seemed out of proportion to their theoretic appendical origin.

*Spleen.*—The walls of the multiloculated cysts were similar to the thickened hyaline splenic capsule. Lining both were single and multiple layers of pleomorphic epithelial cells which did not invade the hyaline wall. In one area (fig. 8), the mucoid exudate could be seen to break through the capsule and into the splenic pulp at two points. This was the only place in all the histologic sections in which an organ had been invaded beyond its surface.

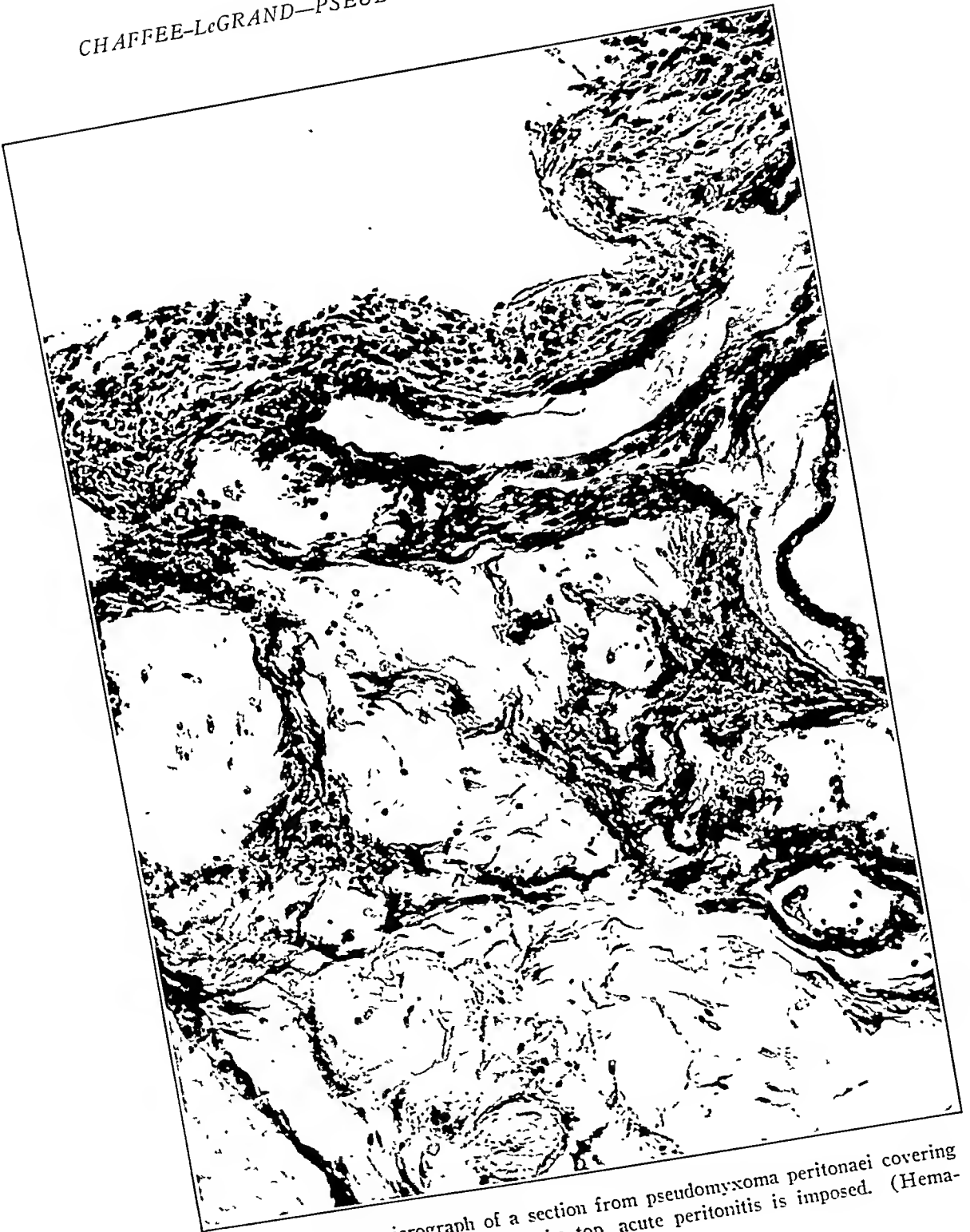


Fig. 6.—Photomicrograph of a section from pseudomyxoma peritonaei covering the serosa of the large bowel: at the top, acute peritonitis is imposed. (Hematoxylin-eosin stain;  $\times 450$ .)

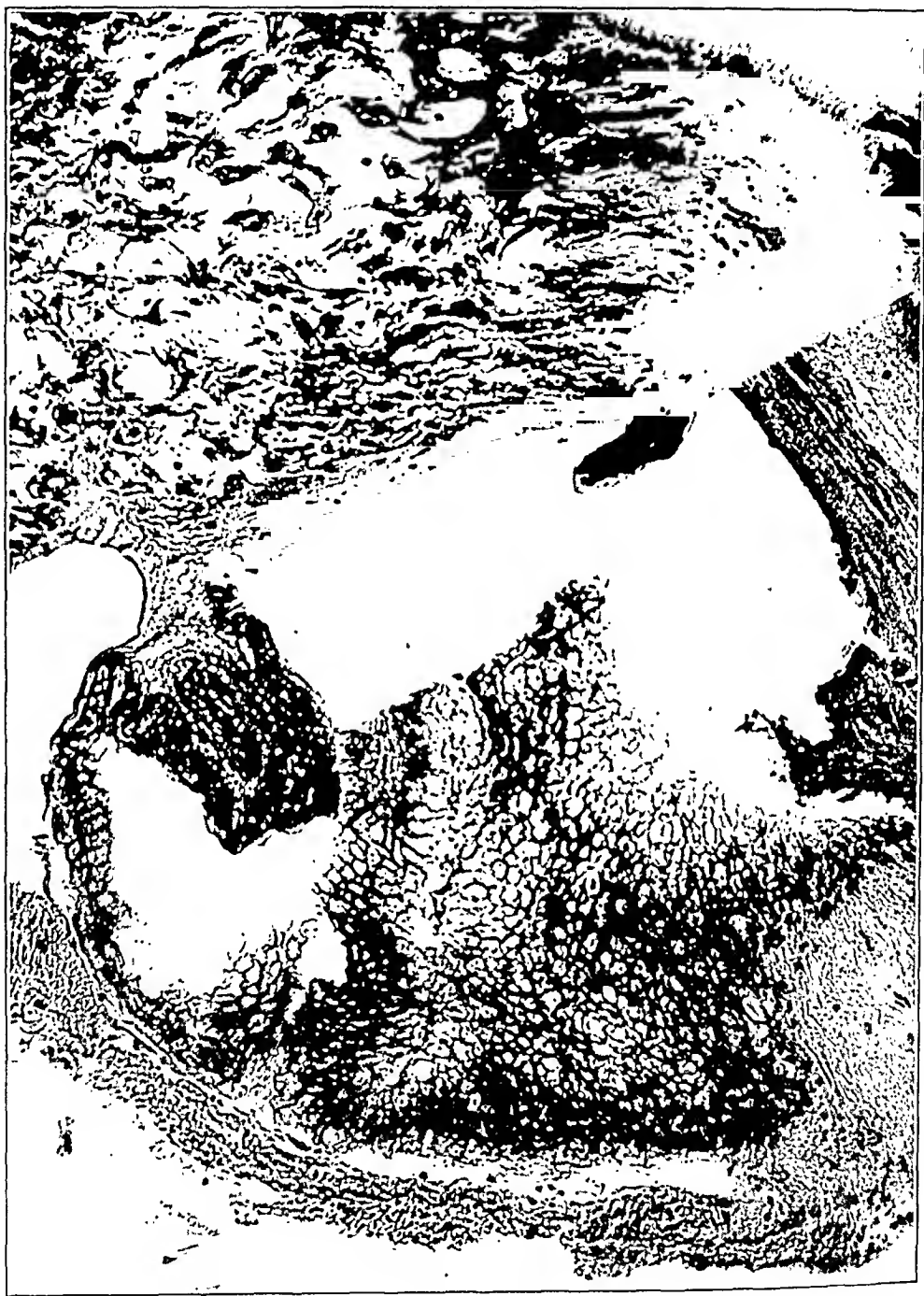


Fig. 7.—Photomicrograph of a section from pseudomyxoma peritonaei on the exterior of the large intestine showing anaplastic tendency of cells and vacuolation. (Hematoxylin-eosin stain;  $\times 450$ .)



Fig. 8.—Photomicrograph of a section of the spleen showing mucoid exudate penetrating the capsule and extending into the pulp. (Hematoxylin-eosin stain;  $\times 450$ .)

## COMMENT

We cannot be certain that this cell anaplasia indicated a definitely histologically malignant process and will grant that pathologists might well differ in their impressions. That cells from a benign appendical mucosa can be implanted on the peritoneum, grow, secrete and produce cells is evident. That they can become malignant, even though their appendical source remains benign, has been less well understood and offers material for hypotheses.

Any evidence of malignant degeneration is largely one of academic interest in this case. The actual cause of death was a series of related events, namely, perforation of the appendical stump, peritonitis and ileus. It is amazing that this patient could have survived so long with such extensive peritoneal growth, and it is conceivable that he otherwise would have succumbed to compression of the bowel or the mesenteric vessels by the myxomatous material.

## TREATMENT

Whether mucocele of the appendix progresses to pseudomyxoma peritonaei or not, the treatment for both conditions is appendectomy. Most operators manually extract as much of the myxomatous material as possible while operating in the peritoneum so that cachexia will not result from too much protein absorption. Closing the abdomen without drainage is advised to reduce the chance of contamination of a peritoneum already reduced in resistance.

Spontaneous rupture of the appendical stump which occurred in our case may serve as a warning to others. During the formation of a mucocele, the tension put on, and the stretching required of, the appendical wall from intraluminal distention may result in a portion of the cecum being drawn toward the appendix in conelike fashion to serve as its proximal attachment. If one then performs an appendectomy in the usual manner, a portion of the cecum is actually cut and ligated. Then after appendectomy, the evaginated cecum tends to assume its previous state, and the tension put on the ligating sutures jeopardizes the integrity of the operative closure. This is undoubtedly what occurred in our case, since no gangrene or necrosis of the stump was found.

Mulsow<sup>26</sup> reported a case in which gangrene of the cecum and the proximal part of the appendix had occurred from invagination of the mucocele into the cecum. These experiences along with the poor tone and color of the bowel noted in our case warn that trouble may be expected in the region of the cecum. With this in mind, Jones and Carmody<sup>23</sup> designed a special operation for mucocele of the appendix.

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26. Mulsow, F. W.: Mucocele of the Appendix with Diverticulum and Invagination into the Cecum, *Tr. Chicago Path. Soc.* **13**:434, 1931.

It consists in removing the lower dependent portion of the cecum, including the appendix, between Payr clamps in such a way that the normal opening of the ileum into the cecum is maintained. Then a Parker-Kerr basting stitch is used to close the opening in the cecum. The reader is referred to the splendid diagrams in the paper of Jones and Carmody.

Finally, roentgen irradiation in cases of pseudomyxoma peritonaei following appendectomy is almost universally advocated. Weaver<sup>8</sup> recommended starting radiation therapy thirty days after operation. His dosage was a series of fourteen treatments totaling 1,386 r over the abdomen and 1,192 over the pelvis divided among twenty-five days.

#### SUMMARY

The fifteenth case to be recorded of pseudomyxoma peritonaei from mucocele of the appendix occurring in a man is reported.

Although ovarian cystadenoma is the common source of pseudomyxoma peritonaei, mucocele of the appendix should not be overlooked.

Pathologically, the neoplastic tendencies, the mortal potentialities and a comparison of the appendical and ovarian origins of pseudomyxoma peritonaei are discussed.

There are no reliable diagnostic clinical features of either mucocele of the appendix or pseudomyxoma peritonaei. Peritoneoscopy was an aid to diagnosis in this case.

The prognosis of simple mucocele of the appendix with appendectomy is good. Cecectomy, to include the dependent part of the cecum and the appendical attachment, is a rational procedure.

Appendectomy and postoperative irradiation should be done in cases of pseudomyxoma peritonaei. The prognosis, however, is grave. The complications and the cause of death in cases of pseudomyxoma peritonaei are of mechanical origin and are not dependent on the presence of malignant cell characteristics.

Drs. W. P. Belk and E. T. Crossan gave valuable suggestions in the preparation of this paper.

# ABSORPTION OF SURGICAL GUT (CATGUT)

## III. DURATION IN THE TISSUES AFTER LOSS OF TENSILE STRENGTH

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In previous communications, the decline and the duration of the tensile strength of surgical gut (catgut) in the tissues<sup>1</sup> and in acid-pepsin solution<sup>2</sup> were reported. An important aspect of absorption of surgical gut is the length of time required for complete absorption after the loss of useful holding power in the tissues. Bates<sup>3</sup> made observations on the absorption of the plain and the chromic catgut of various sizes of one manufacturer. Bower, Burns and Mengle<sup>4</sup> carried out studies on the absorption of two different sizes of catgut of another manufacturer. These experimental studies were made over relatively short periods and were not necessarily designed to follow the ultimate fate of the catgut.

It has been observed clinically at secondary operations through healed incisions that chromic catgut of some varieties may sometimes be readily identified months after it was originally placed in the wound. Also, it has been a clinical observation that chromic catgut of some types may lead to a draining sinus in the operative wound which does not heal over completely until a bulky knot of catgut is extruded or removed

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From the Department of Surgery, the University of Chicago School of Medicine.

This work was aided in part by a grant from the Council on Pharmacy and Chemistry of the American Medical Association.

1. Jenkins, H. P., and Hrdina, L. S.: Absorption of Surgical Gut (Catgut): I. The Decline in Tensile Strength in the Tissues, *Arch. Surg.* **44**:881 (May) 1942.

2. Jenkins, H. P., and Hrdina, L. S.: Absorption of Surgical Gut (Catgut): II. Pepsin Digestion Tests for Evaluation of Duration of Tensile Strength in the Tissues, *Arch. Surg.* **44**:984 (June) 1942.

3. Bates, R. R.: Absorbability of Catgut, *Am. J. Surg.* **43**:702, 1939.

4. Bower, J. O.; Burns, J. C., and Mengle, H. A.: The Superiority of Very Fine Catgut in Gastrointestinal Surgery, *Am. J. Surg.* **47**:20, 1940.

as late as a month or two after operation. These observations have generally been attributed to an abnormal delay in the absorption of the chromic catgut.

It has likewise been observed by many surgeons that clean operative wounds which disrupt within six to ten days may reveal only shreds or fragments or possibly no trace at all of the so-called twenty day chromic catgut originally used in the closure of the wound. This apparently premature absorption has been attributed to various causes. An analysis of the factors entering into abdominal wound disruption with special emphasis on the suture material involved has been previously presented.<sup>5</sup> In an endeavor to obtain a comprehensive view of the ultimate absorption after the loss of tensile strength of the various sorts of surgical gut available, a large number of experimental implants were made in the abdominal muscles of dogs. A limited number of clinical observations were also made from specimens obtained at autopsy or from secondary operations on patients. To facilitate evaluation of the gross condition of the surgical gut in the tissues, the Spalteholz method of preparing cleared tissue specimens was used (this method was also used by Bower, Burns and Mengle<sup>4</sup>). The condition of the catgut was further checked by microscopic sections.

#### EXPERIMENT

The surgical gut of ten different manufacturers was used in sizes no. 2 to no. 000. This represented essentially the same products as those subjected to the previously reported tests of duration of tensile strength in the tissues and in acid pepsin. Each dog was anesthetized with ether, and the abdomen was prepared for operation by shaving and painting with tincture of iodine. Asepsis was maintained with the aid of sterile towels, split sheets and gowns and gloves as well as face masks and caps for the operators. The instruments were autoclaved, and the knives, the scissors and the tubes of catgut were sterilized by a solution of phenol, which was subsequently washed off with alcohol.

The incision was made in the skin and the subcutaneous tissue, exposing the fascia of the rectus abdominis muscle. The incision was made either lateral or mesial to the part of the rectus muscle in which it was intended to implant the catgut. This was done to avoid any difficulties which might arise because of poor healing of the skin immediately above a catgut implant. The catgut was implanted in the rectus muscle at right angles to the direction of the muscle fibers with the aid of an ordinary curved noncutting needle. After removal of the needle, the free ends were tied by a triple throw square knot. The excess catgut beyond the knot was cut off. It was feasible to have as many as 15 to 25 implants in each of the rectus muscles, depending on the size of the animal. The flap of skin and subcutaneous tissue was then replaced over the line of implants, and the subcutaneous tissue was sutured to the underlying muscular fascia either lateral or mesial to the row of implants, in whichever position it would seal off the implants from the rest of the wound. The skin was then closed with a continuous subcuticular suture of silk reenforced by interrupted sutures when necessary.

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5. Jenkins, H. P.: A Clinical Study of Catgut in Relation to Abdominal Wound Disruption, Surg., Gynec. & Obst. **64**:648, 1937.



A varied combination of the different sorts of surgical gut was used in these experimental animals to obtain as much diversification as possible as well as to obtain controlled observations. To permit subsequent identification of the sutures used, it was customary to adopt a certain standard sequence of implantation from upper to lower portions of the rectus muscle. The different sizes from no. 2 to no. 000 of any particular type of catgut were implanted from above downward. The twenty day type of chromic catgut was implanted above the forty day type. Products of different companies placed in the same animal were implanted from the upper to the lower part of the abdomen in the sequence of company 1, company 2 and so on.

In most instances, several sets of implants were made in different animals from the same tubes of surgical gut. In one series of animals, a set of implants was made in one rectus muscle and then at a subsequent date, usually twenty days later, another set of implants from the same tubes of gut used previously were implanted in the other rectus muscle. Whenever catgut was carried over from one operation to another at a later date, it was kept sterile by sealing in individual glass tubes in 95 per cent alcohol. In some instances, implants of the boilable variety of surgical gut were compared with implants of the nonboilable type of surgical gut of the same company. Most of the implants, however, were made with nonboilable surgical gut.

The animals were permitted to survive for varying lengths of time up to a year or more. Usually, they were killed by electrocution. The abdominal wall was then excised after removal of the overlying skin. In a few instances, the animals were reoperated on; the rectus muscles were excised, and the abdomen was closed. The specimens were fixed in 10 per cent solution of formaldehyde for at least twenty-four hours. The tissues were then bleached in a cold solution of hydrogen peroxide, which was sealed and exposed to sunlight for at least one or two days. Less adequate bleaching was obtained by exposure to artificial light. The specimens were then dehydrated by numerous washes in alcohol for several days. At least two washes in absolute alcohol were usually necessary for adequate dehydration. The tissues were then soaked in benzene for twenty-four hours and finally immersed in methyl salicylate. At this stage, a large number of air bubbles usually became apparent in the specimen and obscured the transparency of the tissues. The bubbles were removed by the aid of a suction pump.

If the bleaching and the dehydration were adequate, a clear yellow or orange transparent tissue specimen was obtained in which the chromic catgut implants could be readily identified if present. Plain catgut could not be readily identified in the tissues by this method except in a few instances. Also, it was difficult to identify one brand of twenty day and forty day tanned catgut in the tissues because it had the general appearance of plain catgut.

An opal glass plate was put behind the specimen, and with the aid of illuminated boxes, the gross condition of the various chromic catgut implants could be studied carefully. The condition of the catgut from the standpoint of its gross appearance was classified on the basis of 10 as follows:

- 10—Intact; no evidence of absorption.
- 9—Ply unraveling but catgut loop and knot intact.
- 8—Knot untied spontaneously but catgut otherwise intact.
- 7—Slight fraying of catgut.
- 6—Break in continuity of catgut.

- 5—Moderate or marked fraying of catgut with or without break.
- 4—Catgut gone except for knot.
- 3—Fragments of catgut remaining.
- 2—Shreds of catgut remaining.
- 1—Trace of catgut remaining.
- 0—Completely gone.

After the gross condition of the catgut was studied, most of the specimens were photographed for a permanent record. In numerous instances, a small block of tissue was cut out for microscopic sections. It was necessary to wash out the methyl salicylate with several changes of benzene. Then the benzene was removed with several changes of absolute alcohol. The block was then ready to be started on the routine preparation for celloidin (pyroxylin) embedding and subsequent cutting for microscopic sections. A number of microscopic sections were also made of the tissues in which catgut was implanted for the tests of duration of tensile strength previously reported.

By this method, 100 experimental specimens were prepared in which approximately 2,000 catgut implants had been placed. In addition, 35 specimens were prepared from clinical material obtained at autopsy or secondary operation. The general behavior of the various sorts of chromic catgut which were implanted in the tissues can be ascertained by reviewing the photographs of the cleared tissue specimens representing different periods of tissue absorption. In addition to the gross appearance in the tissue of the chromic catgut implants, the microscopic studies of the condition of the catgut and the reaction of the tissues about it provide a number of observations of considerable interest.

The designation of the various brands of catgut as those of company 1, company 2 and so on is purely arbitrary. The method of labeling the catgut as twenty day chromic or forty day chromic is used in this presentation although attention is drawn to the nomenclature of catgut which has been officially approved by the Committee of Revision of the United States Pharmacopeia:

U. S. P. Terminology	Terminology Formerly in Use
Type A—Plain surgical gut (untreated)	Plain catgut
Type B—Mild chromic surgical gut (mild treatment)	Ten day chromic catgut
Type C—Medium chromic surgical gut (medium treatment)	Twenty day chromic catgut; medium hard chromic catgut, ten to twenty day
Type D—Extra chromic surgical gut (prolonged treatment)	Forty day chromic catgut; extra hard chromic catgut, thirty to forty day

## RESULTS

A number of variable aspects of the absorption of surgical gut were encountered. There was often an appreciable variation in the rate of absorption of surgical gut in the different experimental and clinical specimens examined. Although the magnitude of variation was considerable in some instances, nevertheless, the large number of specimens available for study permitted reasonably accurate observations on the relative rate of absorption and the average length of time required for complete absorption of the different sorts of surgical gut.

In regard to the relative differences in the rate of absorption, it was found that the smaller sizes of chromic catgut of some of the companies were absorbed more slowly than larger sizes (fig. 2). In other products the rate of absorption of the various sizes was more or less uniform (figs. 1 and 3), although in still other products the smaller sizes were more rapidly absorbed than larger sizes (fig. 4, companies 3 and 5). Exceptions were observed in regard to the various sizes of catgut which were inconsistent with any of the three general trends of behavior already mentioned. The differences in the rate of absorption of the chromic catgut of the various companies was of a greater magnitude than was observed between the twenty day and the forty day chromic catgut (types C and D) of any one company (fig. 4).

The behavior of any particular size, type or brand of catgut from any individual lot was usually fairly consistent, although instances of

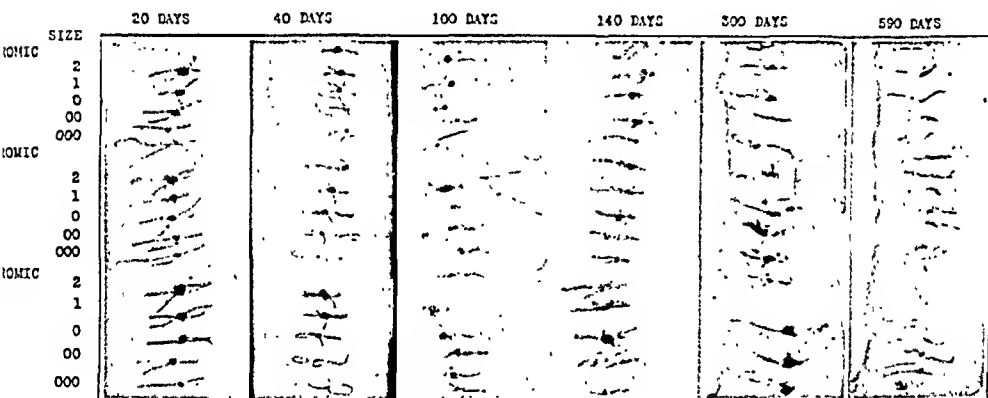


Fig. 1.—Photographs of cleared muscle specimens showing the gross appearance of chromic catgut (company 1) implants in the tissues (series 1937). At the end of twenty or forty days there appears to be no conspicuous evidence of absorption of the chromic catgut regardless of whether the ten day, the twenty day or the forty day type (now called types B, C and D, respectively) was used. Specimens of sixty and eighty days' duration, which are not shown here, did not differ appreciably in their gross appearance from the forty day specimen. The one hundred day specimen shows evidence of beginning absorption, which is fairly well advanced in the one hundred and forty day specimen, as evidenced by the blurred outline of catgut implants. Photomicrographs of the catgut at about this stage of absorption show that the gross appearance is somewhat misleading as far as judging the amount of catgut which remains unabsorbed, because at this stage the catgut has been broken up by the phagocytic cellular response. During this stage, the fragments of the chromic catgut become engulfed in the phagocytic cells, and as the fragments are destroyed, the cytoplasm of the cells apparently takes on the dark green or brown color of the collagen chromate. Dense accumulations of these cells will therefore give a gross appearance which simulates an undigested portion of chromic catgut. In the five hundred and ninety day specimen there still persists some evidence of the chromic catgut implants, but these are residual accumulations of chromic-stained phagocytic cells.

appreciable variation were observed in the surgical gut from identically labeled lots obtained from time to time from the same company. (The term "lot" refers to a sealed box of surgical gut bearing the serial number characteristic of the particular company.)

The absorption of surgical gut from the gross morphologic standpoint was generally classified as rapid or slow. In addition an intermediately absorbed category was sometimes distinguished.

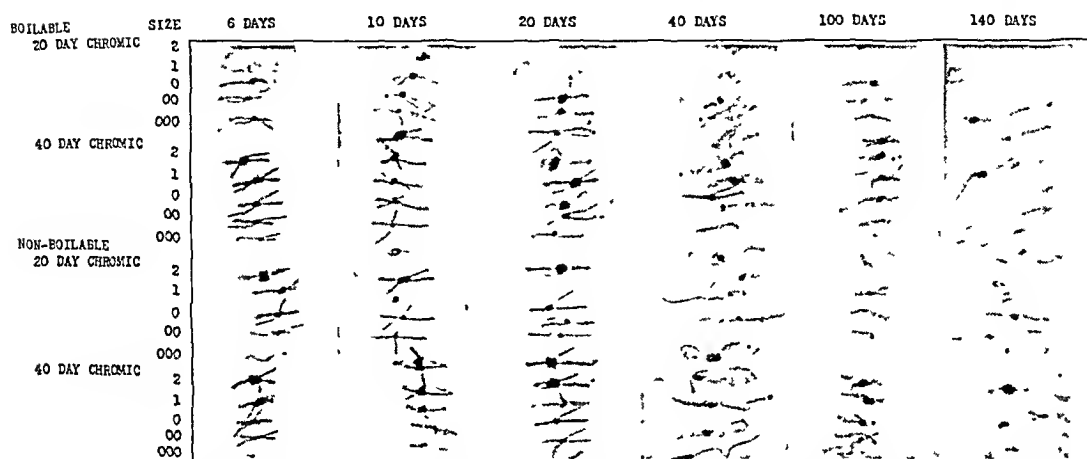


Fig. 2.—Photographs of cleared muscle specimens showing the gross appearance of chromic catgut (company 2) implants in the tissues (series 1937). In the six day specimen it will be observed that all the implants are intact except two. The no. 1 size of twenty day chromic catgut has been practically completely absorbed. The no. 2 size of twenty day chromic catgut has been absorbed except for the knot. In the ten day specimen, most of the implants are to be found intact except as follows: The no. 2 size of twenty day chromic catgut in the boilable series is completely absorbed. The no. 1 size, which is adjacent, is absorbed except for the knot. In the nonboilable series the no. 2 size of the twenty day chromic catgut is absorbed except for fragments of the knot. The no. 0 size of twenty day chromic catgut shows evidence of considerable absorption. In the twenty day specimen, the no. 2 and no. 1 sizes of twenty day boilable chromic catgut are completely absorbed. The no. 2 and no. 0 sizes of forty day chromic catgut are showing some evidence of absorption. In the nonboilable series, the no. 1 size of twenty day chromic catgut is completely absorbed. A tendency for the plies to separate can be detected in the no. 2 size of forty day chromic catgut although the implant is intact. In the forty day specimen there is evidence of considerable absorption. In the one hundred day specimen, the catgut has apparently been less rapidly acted on by the tissues than the forty day specimen would lead one to presume. The no. 2 and no. 1 sizes of twenty day chromic catgut of both the boilable and the non-boilable series have been completely absorbed. The other implants are in a beginning or a moderately advanced stage of absorption which is comparable to some extent to that observed for the catgut of company 1. In the one hundred and forty day specimen, it is difficult to identify the various implants accurately. A fairly advanced stage of absorption is obviously present. Microscopic sections of the one hundred and twenty day specimen show that the catgut has not as yet been broken up to any marked degree by the phagocytic cells.

Most brands of plain catgut were considered as representing rapidly absorbed suture material. In certain chromic catgut products, advanced stages of absorption were observed within ten days, although the catgut was labeled twenty day chromic (fig. 2). Complete absorption of this variety of what was termed rapidly absorbed catgut was usually accomplished within one to three weeks (figs. 8 and 9).

Any particular chromic catgut which could be demonstrated to be intact and free from gross evidence of absorption beyond ten days was usually not completely absorbed for a long time. This constituted the slowly absorbed variety of catgut. The length of time required for complete absorption was generally between three and six months and in some instances longer (figs. 1, 2, 3 and 5). Although in the gross specimens there appeared to be evidence of unabsorbed chromic catgut

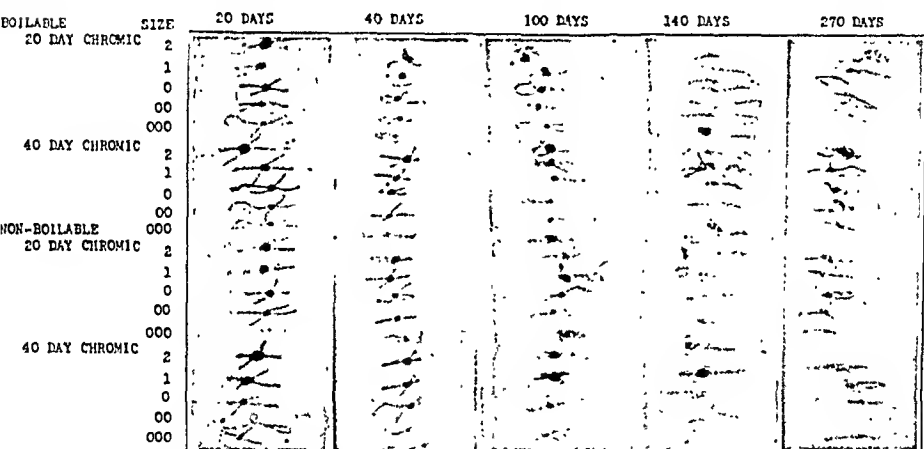


Fig. 3.—Photomicrographs of cleared muscle specimens showing the gross appearance of chromic catgut (company 4) implants in the tissues (series 1937). At the end of twenty days, the implants appear to be relatively intact throughout except for the no. 000 size of twenty day chromic catgut of the nonboilable series. This is almost completely absorbed. The no. 00 size of forty day chromic catgut in this group appears to have untied spontaneously, and there seems to be a break in the continuity of some of the no. 000 sizes of chromic catgut. In the forty day specimen there is little general change from that observed in the twenty day specimen. Two of the no. 000 size sutures and 1 of the no. 00 sizes appear to be fairly well absorbed. In the one hundred day specimen there is evidence generally of beginning break-up of the catgut. The smaller sizes are definitely less conspicuous than the larger sizes, and the latter show a blurring of the outline of the catgut. In the one hundred and forty day specimen, the catgut implants show a rather uniformly advanced stage of absorption which is characterized histologically by fragmentation and destruction of the catgut by the phagocytic cells. In the two hundred and seventy day specimen, the apparent persistence of the chromic catgut implants is due to residual accumulations of chromic-stained phagocytic cells.

for considerably longer than six months, this observation was usually due to a chromic-colored staining in the tissues in the location of the

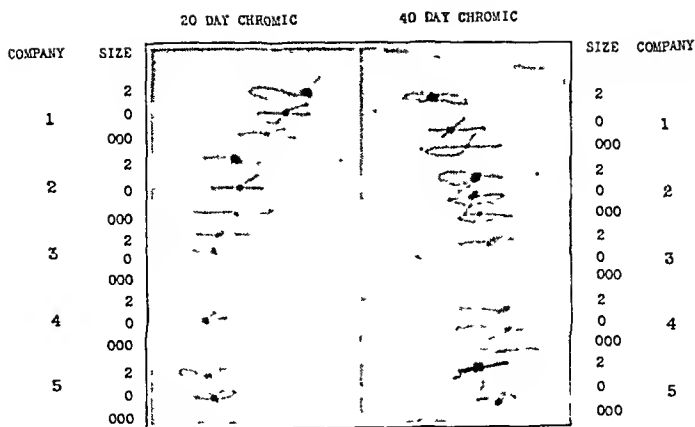


Fig. 4.—Photographs of cleared muscle specimens showing the gross appearance of chromic catgut implants after twenty days in the tissues (series 1939-1940, dog 792). The sutures of company 1 are all intact. The no. 2 size of the twenty day and the forty day chromic catgut of company 2 shows evidence of some disintegration. The no. 000 size of company 3 appears to be completely absorbed; the no. 0 size, moderately absorbed, and the no. 2 size, beginning absorption. The no. 2 and the no. 000 sizes of the twenty day chromic catgut of company 4 are almost completely absorbed, while the no. 0 size is relatively intact; the forty day chromic catgut is moderately absorbed. The no. 000 size of the chromic catgut of company 5 is completely absorbed, although the larger sizes show little evidence of absorption. The smaller sizes of chromic catgut of companies 3 and 5 are fairly rapidly absorbed. The larger sizes of company 2 are more rapidly absorbed than the smaller sizes. The sutures of company 1 have fairly uniform absorption; those of company 4 have rather inconsistent absorption.

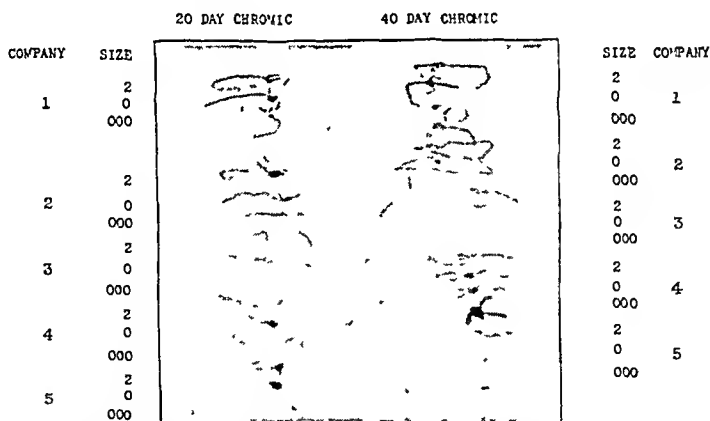


Fig. 5.—Photographs of cleared muscle specimens showing the gross appearance of chromic catgut implants after one hundred days in the tissues (series 1939-1940, dog 727). A moderate amount of the suture material of company 1 appears to be present; a less conspicuous amount of the suture material of company 2 is left, and only a trace of the suture material of company 3 remains. The no. 0 size of the twenty day chromic catgut of company 4 and all sizes of the forty day chromic catgut of company 4 show up fairly well. The no. 2 size of the forty day chromic catgut of company 5 appears to be the best preserved suture of the series; the no. 2 and the no. 0 sizes of the twenty day and the no. 0 size of the forty day chromic catgut of company 5 show up fairly well. (Microscopic sections show moderate or slight evidence of absorption comparable to that shown in the photomicrographs in figure 13.)

implant rather than to chromic catgut which had not been absorbed (figs. 1, 3 and 6). This point will be discussed further in connection with the microscopic studies.

The intermediately absorbed variety of catgut was not necessarily a clearcut entity but appeared to represent a variety of surgical gut which remained intact for about ten days and underwent complete absorption within approximately three weeks to three months. Some of the plain catgut which was studied during the course of this work on the absorption of surgical gut was considered as intermediately absorbed catgut. Also, certain sizes of several brands of chromic catgut appeared to fall within this classification. In some instances, this relatively slowly absorbed or intermediately absorbed variety of surgical gut

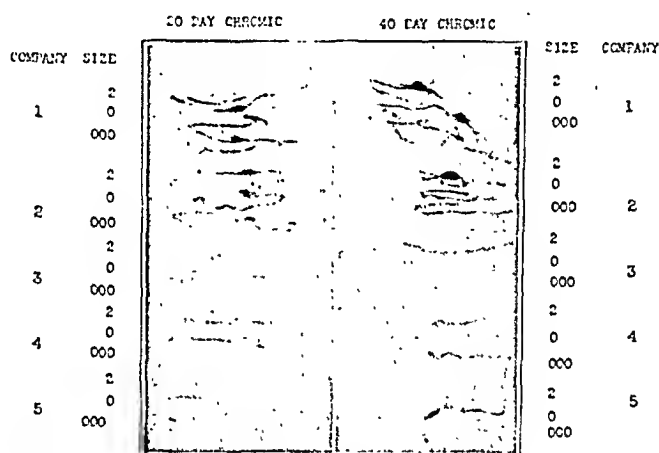


Fig. 6.—Photographs of cleared muscle specimens showing the gross appearance of chromic catgut implants after one year in the tissues (series 1939-1940, dog 791). The suture materials of companies 1 and 2 appear to be present. There are faint traces of the suture material of company 3; there is slightly more evidence of a trace of the suture material of company 4. There is a faint trace of the twenty day chromic catgut of company 5; size 2 of the forty day chromic catgut is noticeable. (Microscopic sections show only clusters of macrophages comparable to those demonstrated in figure 14.)

underwent a rate of absorption comparable to that observed for the rapidly absorbed type of catgut.

From the standpoint of microscopic studies, the absorption of surgical gut was divided into two phases of cellular response on the part of the tissues. The first phase was characterized by a polymorphonuclear leukocytic invasion about the catgut—plain catgut of most varieties (fig. 7) and chromic catgut of certain types (figs. 8 and 9) usually underwent absorption with this kind of cellular response predominating. In this event, the plies of the catgut were invaded, and the catgut was broken up into fragments and shreds by the action of the polymorpho-

nuclear leukocytes. Subsequent to the destruction of the catgut, the cellular response subsided fairly rapidly. Absorption by the leukocytic mechanism was apparently the characteristic aspect of rapid absorption. This was presumably accomplished by a liquefaction of the catgut by enzymes liberated from the leukocytes.

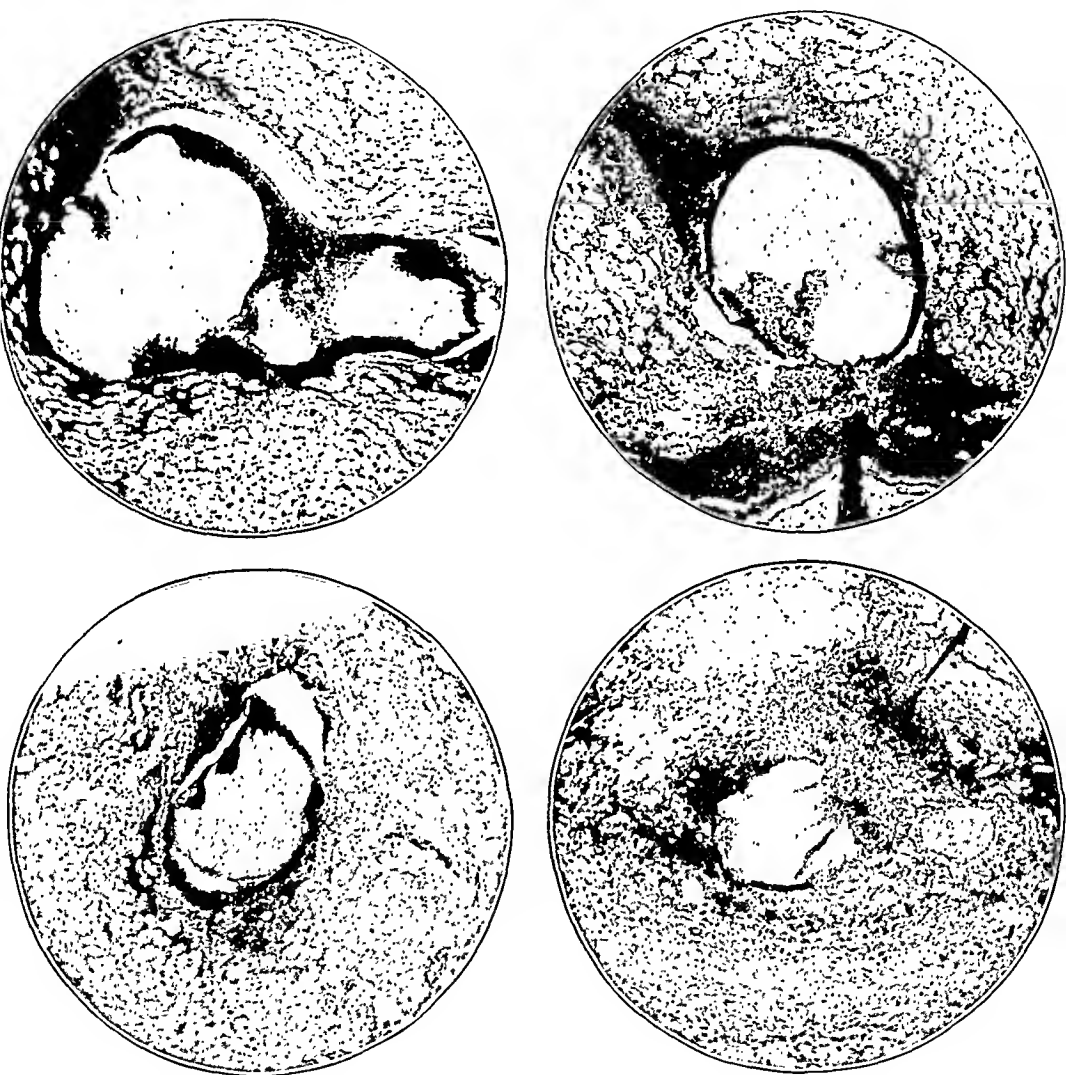


Fig. 7.—Photomicrographs of plain catgut implants after five days in the tissues showing the tissue reaction associated with rapid absorption. There is conspicuous leukocytic response and disintegration of the catgut at this early date evident in all four photomicrographs.

Most varieties of chronic catgut tended to survive the initial polymorphonuclear leukocytic phase. The magnitude of leukocytic response varied considerably in different specimens examined and with certain plain and chronic products. In general, however, most brands of



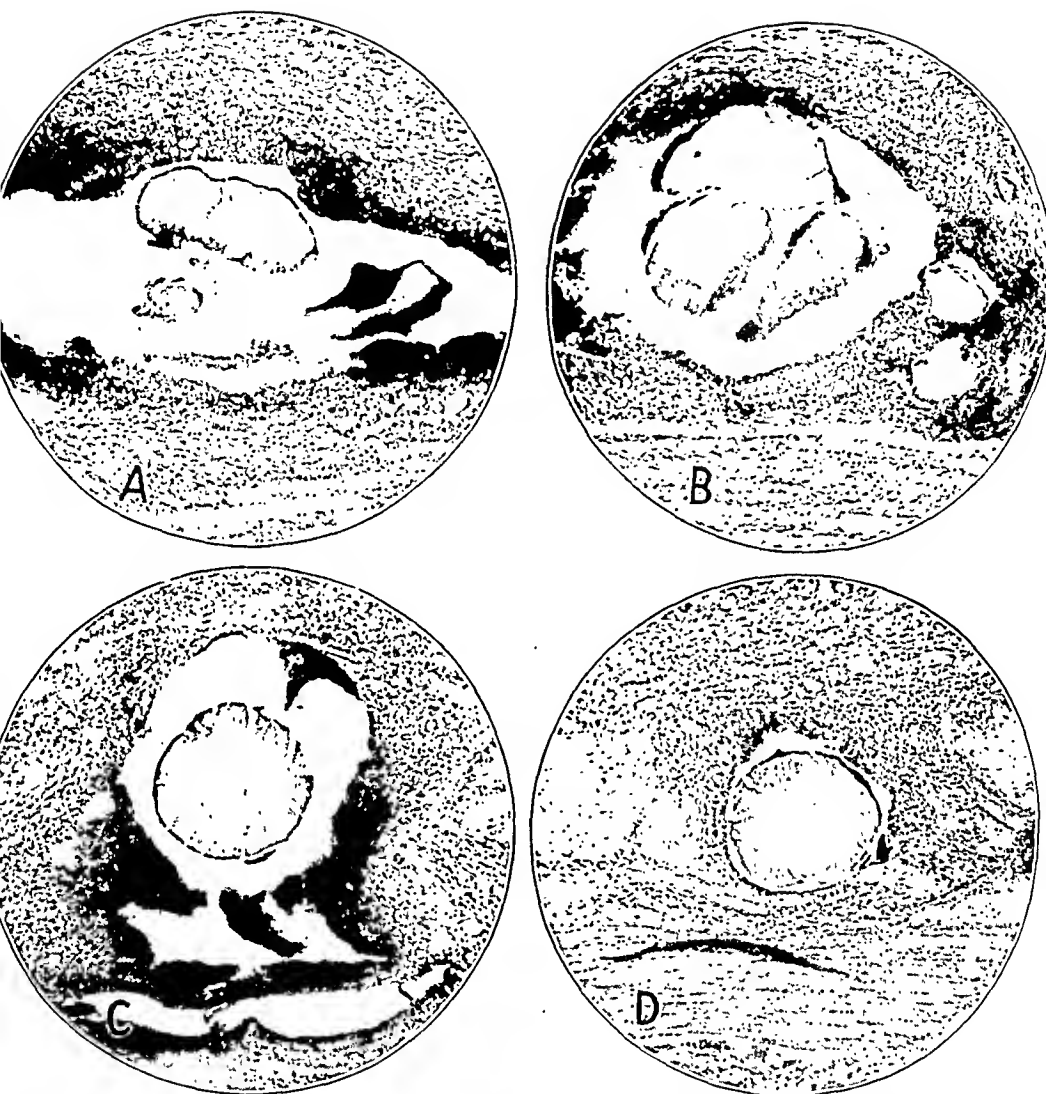


Fig. 8.—Photomicrographs of implants of different sizes of the same brand of chromic catgut (twenty day, company 2) after ten days in the tissues showing the tissue reaction associated with the absorption of chromic catgut.

The conspicuous cellular response seen in these photomicrographs consists mainly of polymorphonuclears, although many macrophages also have accumulated about the catgut. The no. 2 and no. 0 sizes show considerable evidence of disintegration, although the no. 00 and no. 000 sizes appear to be intact. The leukocytic response may subsequently subside, leaving only the macrophages, which have a relatively slow action on the catgut. However, it is probable that the leukocytes will be responsible for most of the absorption of the no. 2 and no. 0 sizes. Whatever is left over from the leukocytic absorptive mechanism will then be taken care of by the macrophages. The conspicuous cellular response demonstrated in these photomicrographs is not necessarily characteristic of most varieties of chromic catgut. *A*, no. 2 size; *B*, no. 0 size; *C*, no. 00 size; *D*, no. 000 size.

chromic catgut appeared to elicit a less intense tissue reaction of a leukocytic type than was usually characteristic for plain catgut or certain types of chromic catgut (figs. 9, 10, 11, 12 and 13). The relatively moderate or slight amount of acute tissue reaction observed for most

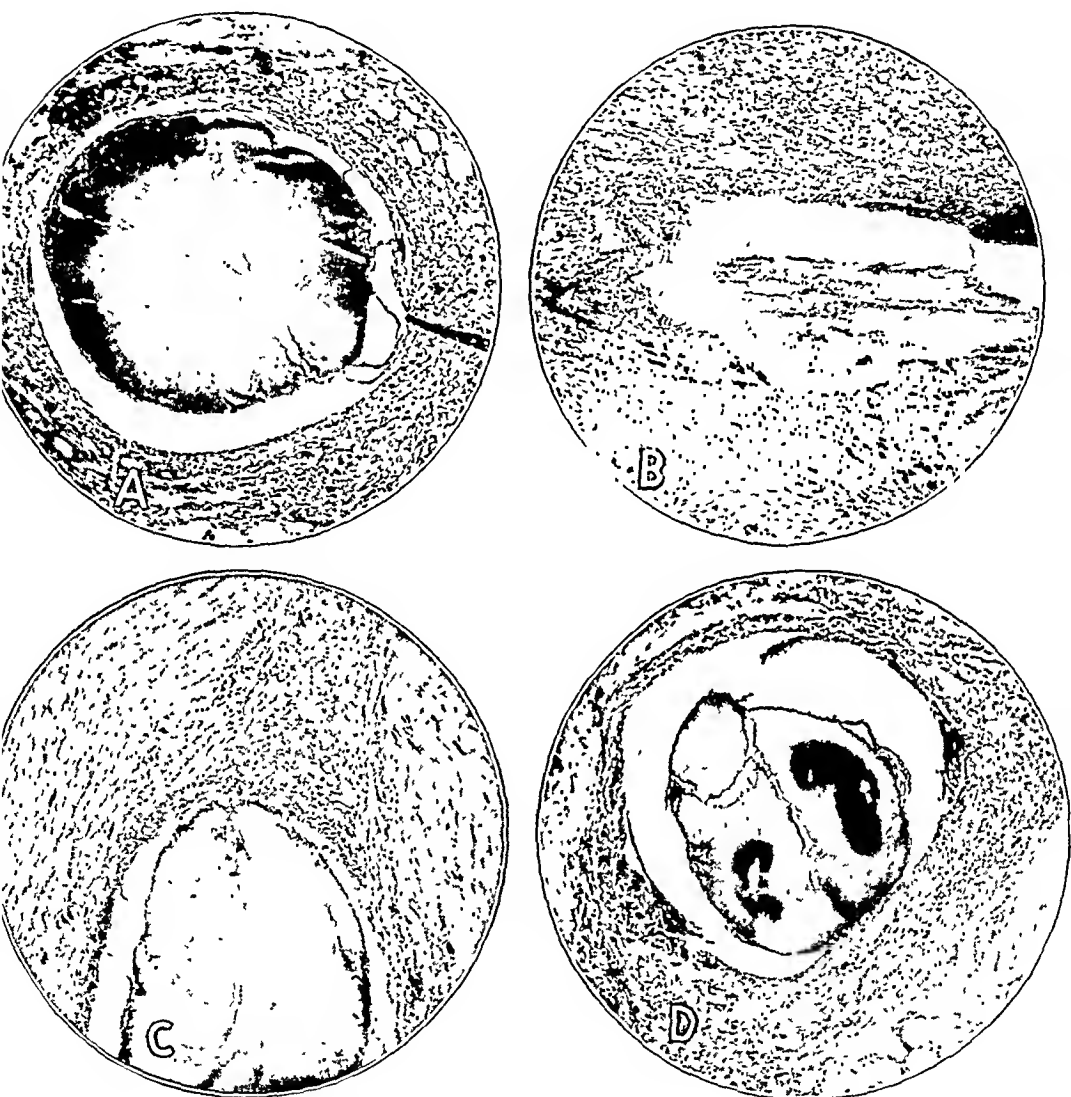


Fig. 9.—Photomicrographs of implants of large size chromic catgut (no. 2) of different brands (twenty day chromic) after ten days in the tissues showing the tissue reaction associated with the absorption of chromic catgut.

In some products (e. g., that of company 2) there is apparently a conspicuous leukocytic response as well as some macrophage response at the end of ten days, although in other products there is relatively slight leukocytic response at this time. Such reaction as does occur appears to be more of a fibroblastic or a macrophage type. The latter response is generally associated with a better state of preservation of the catgut than when leukocytes are present in large numbers. *A*, no. 2 twenty day chromic catgut of company 1; *B*, of company 2; *C*, of company 3; *D*, of company 4.

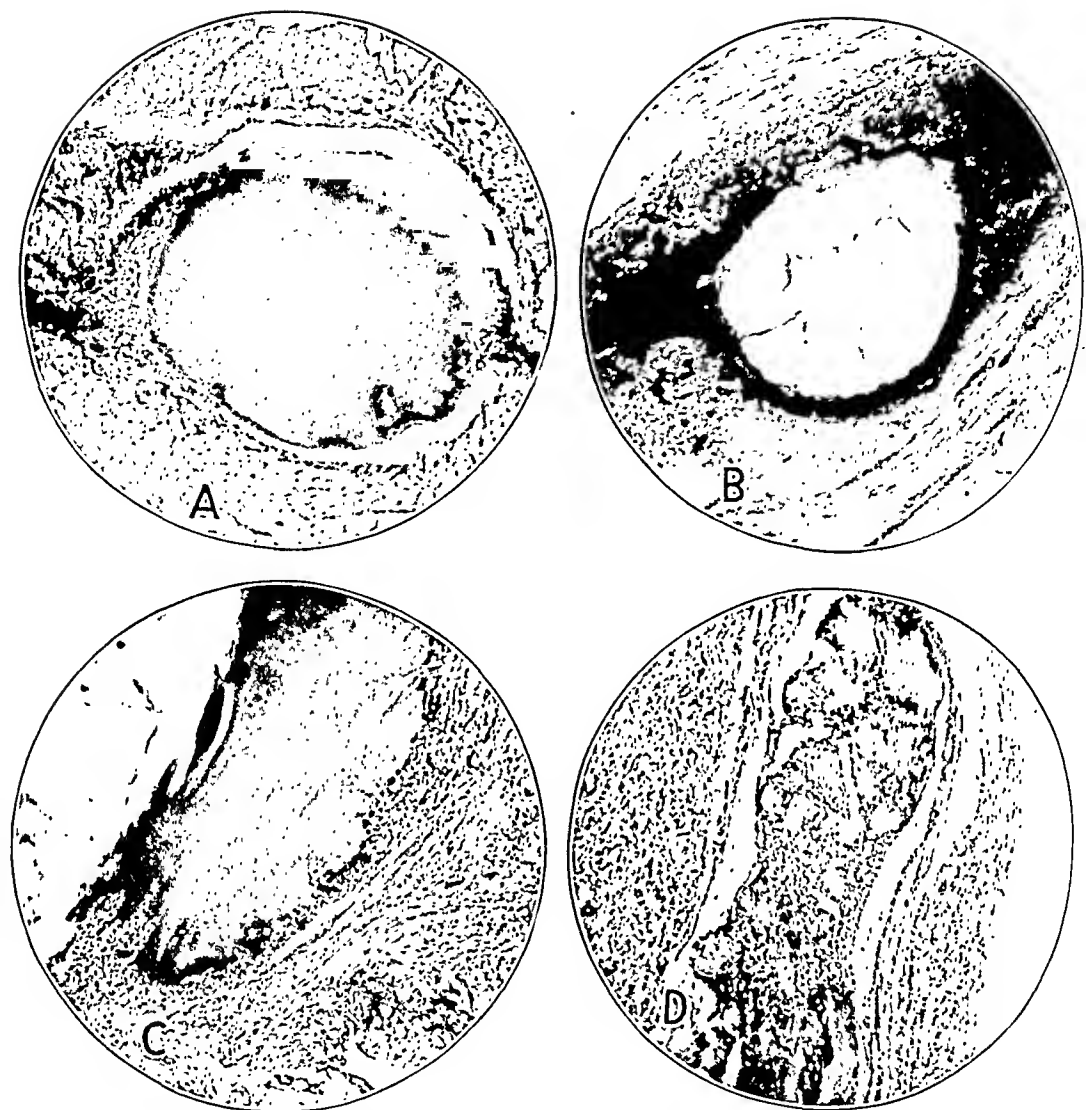


Fig. 10.—Photomicrographs of chronic catgut implants after twenty days in the tissues showing the tissue reaction associated with the absorption of chronic catgut.

The varying tissue response to chronic catgut in the larger sizes (no. 2 and no. 1) is demonstrated by these four photomicrographs of different brands of catgut. The size of the catgut is not per se necessarily the most important factor in the amount of tissue reaction seen, because one may see much more tissue reaction about some of the smaller sizes than will be observed in certain of the larger sizes. Varying stages of absorption of the catgut can be seen. *A*, fibroblastic encapsulation of the catgut and beginning accumulation of macrophages about the periphery. *B*, no apparent evidence of fibroblastic encapsulation; marked leukocytic invasion of tissues about the catgut and early appearance of many macrophages. *C*, irregular areas of absorption along the periphery by macrophages accompanied by scattered lymphocytes and a few polymorphonuclears. *D*, almost complete disintegration of the catgut without evidence of leukocytic response at this time. There is a noticeable fibroblastic response, and occasional macrophages are present.

of the chromic catgut studied constituted a point of considerable importance in this work on the absorption of surgical gut. Aside from the microscopic studies in support of this point there were a large number of gross observations made regarding the amount of exudate character-

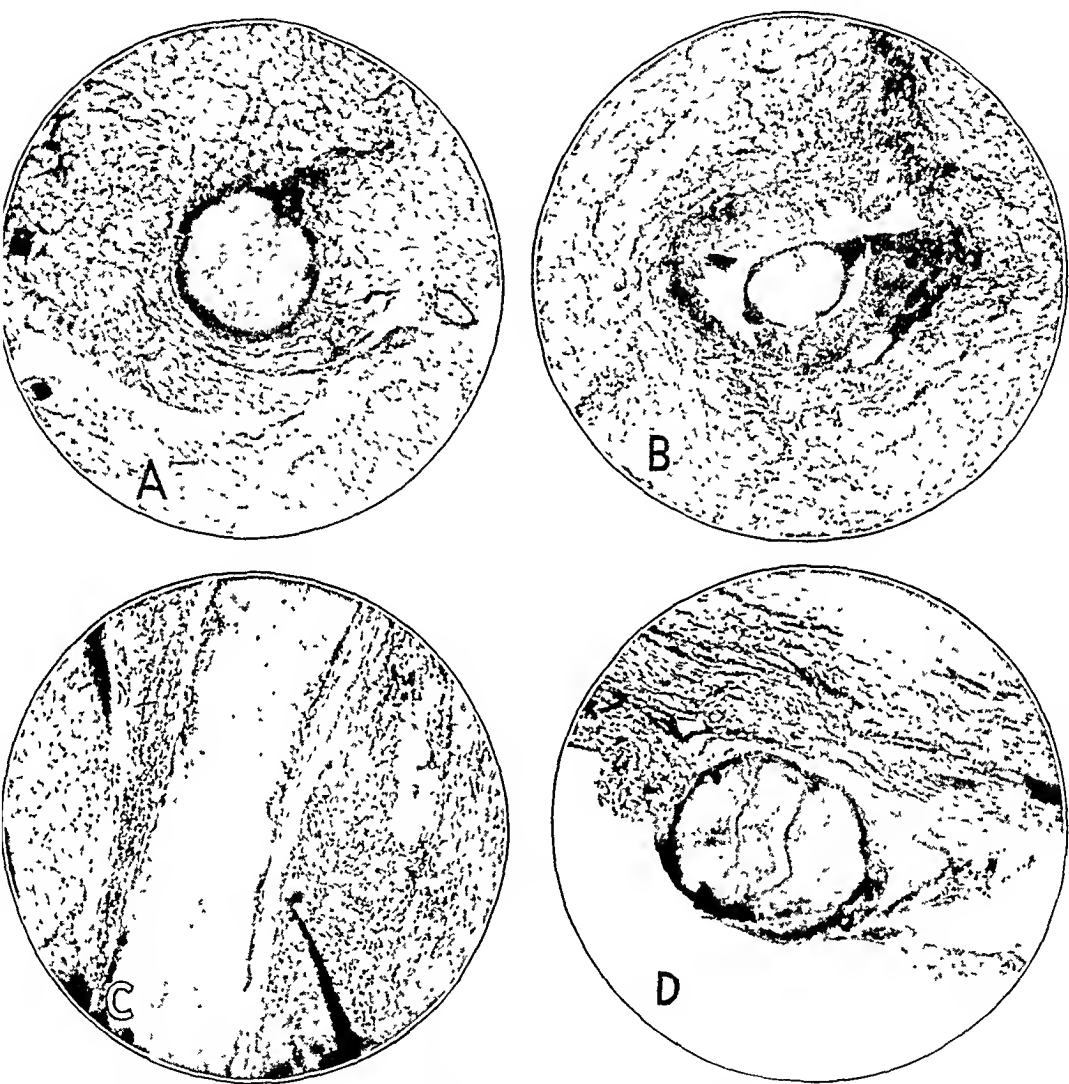


Fig. 11.—Photomicrographs of chromic catgut implants after twenty days in the tissues showing the tissue reaction associated with the absorption of chromic catgut. Absence of appreciable leukocytic reaction in three of the four photomicrographs of different brands of no. 000 size is generally observed for most of the fine sizes of chromic catgut. The conspicuous leukocytic and macrophage reaction seen in one of the photomicrographs is more characteristic of certain products than of chromic catgut in general. *A*, (company 1) moderate fibroblastic response and some macrophages; *B*, (company 2) marked leukocytic and macrophage reaction; *C*, (company 4) relatively slight fibroblastic and macrophage reaction and occasional lymphocytes; *D*, (company 5) relatively slight fibroblastic and macrophage reaction.

istic of the various sizes, types and brands of catgut implanted in the tissues. These observations were made during the course of tensile strength tests previously reported<sup>1</sup> and corresponded with what was observed microscopically.

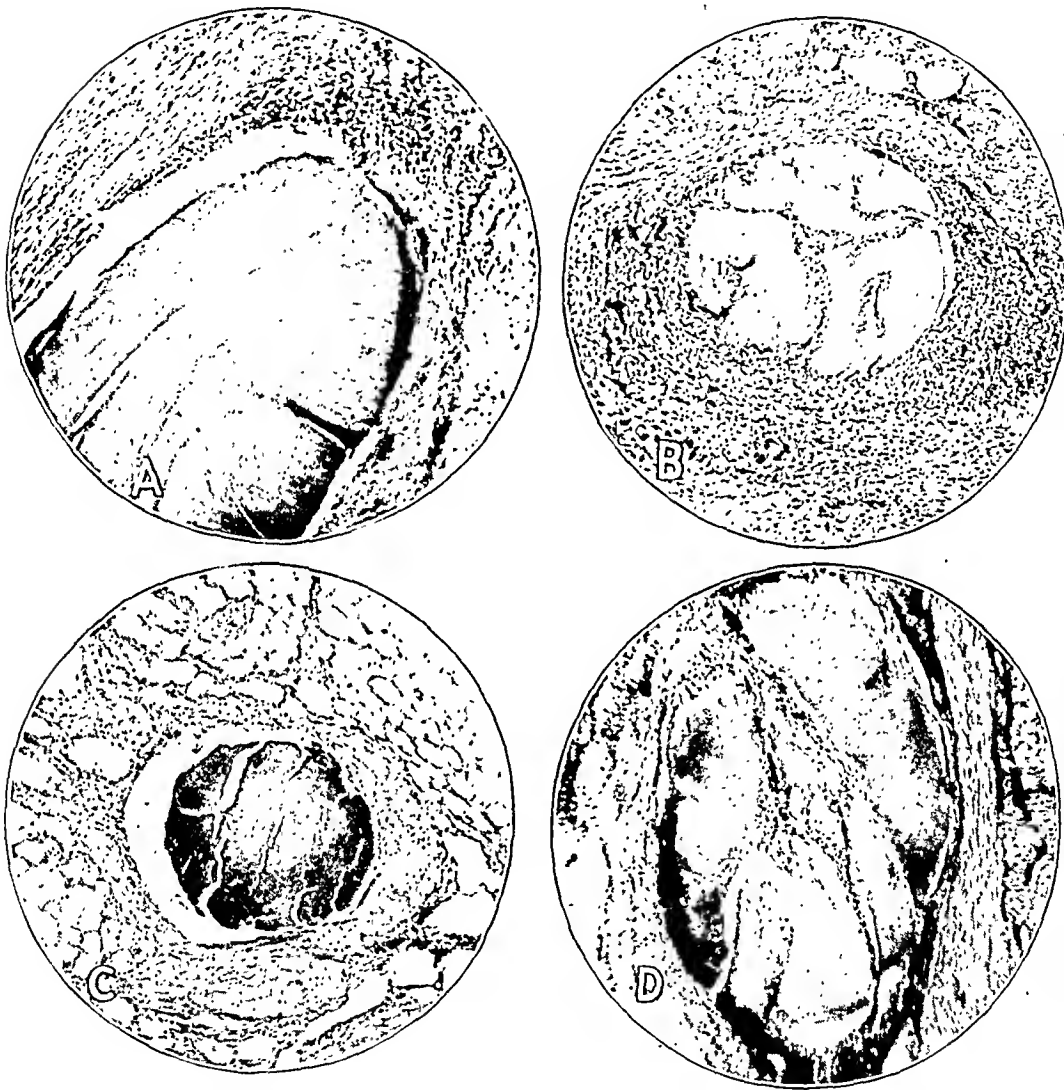


Fig. 12.—Photomicrographs of chronic catgut (no. 0) recovered from patients (at autopsy or reoperation) showing varying amounts of the tissue reaction which is generally observed during the course of slow absorption. *A* (sixteen days), there has been minimal tissue reaction with a few lymphocytes and macrophages; the catgut is intact. *B* (thirty-five days), there has been invasion of the plies of the catgut by macrophages and few lymphocytes; some giant cells are present. *C* (thirty-six days), the cellular response is negligible except for fibroblasts; the catgut is intact. *D* (forty-five days), invasion of the plies of catgut by few macrophages, lymphocytes and fibroblasts has occurred.

The second phase of surgical gut absorption was characterized by the phagocytic activity of macrophages. If the catgut survived the leukocytic phase, the various cell types generally classified as macrophages or histiocytes accumulated about the catgut. The onset of this phase was

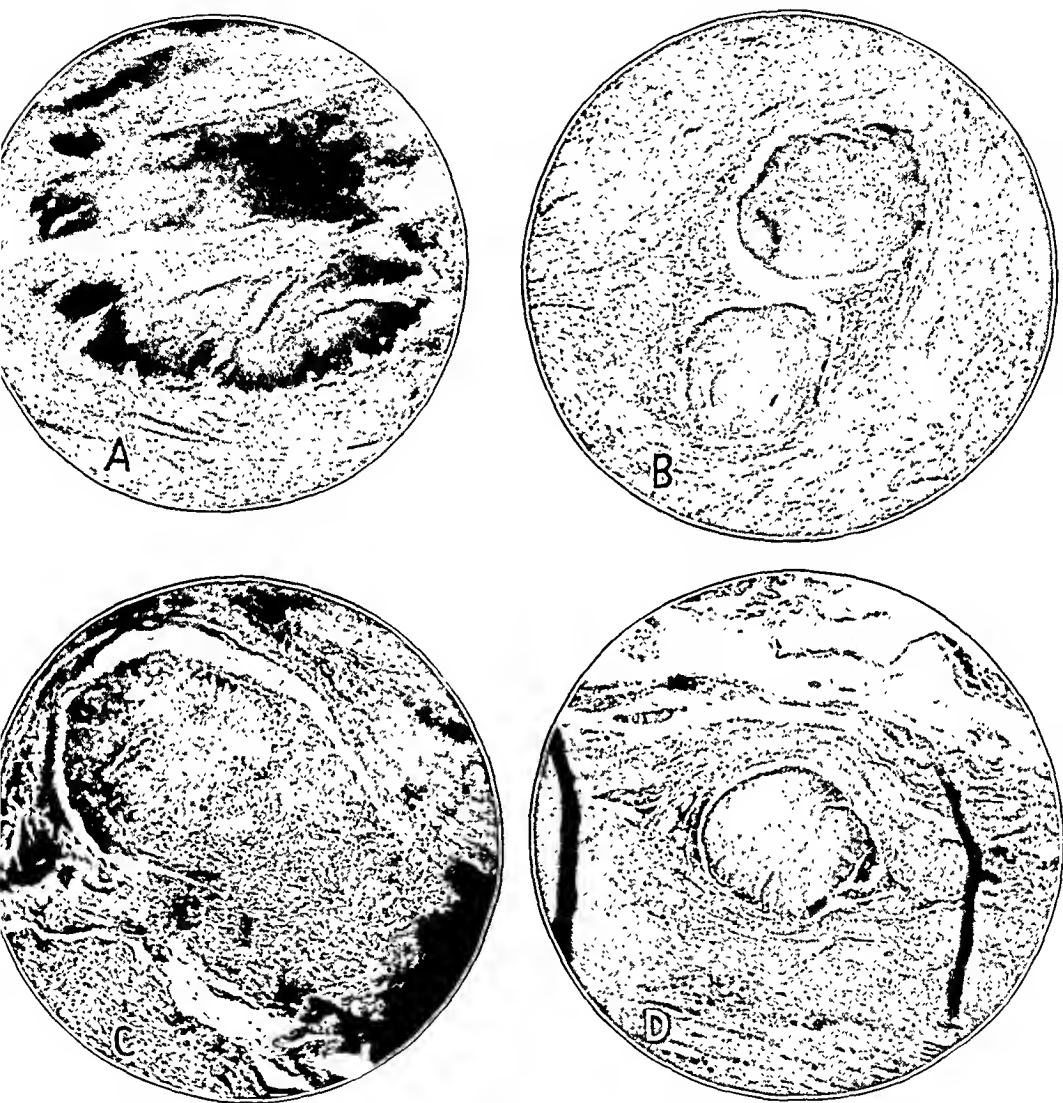


Fig. 13.—Photomicrographs of chromic catgut after three months in the tissues showing the tissue reaction associated with the absorption of chromic catgut. *A* (from autopsy), no. 2 chromic catgut with marked fragmentation and relatively slight cellular reaction. *B* (from autopsy), no. 000 with some invasion of catgut by macrophages. *C* (dog), no. 2 with moderate invasion and destruction of catgut by macrophages but no apparent evidence of leukocytic reaction. *D* (dog), no. 000 catgut which is practically intact, although a few macrophages are accumulating and beginning to invade the strand.

observed as early as in seven to ten days (figs. 8 and 9). There was no sharp transition between the initial leukocytic phase and the secondary macrophage phase. In many instances both phases could be detected, but usually one or the other predominated. Occasionally an intervening period of slight cellular response was observed. Varying amounts of lymphocytic invasion were often associated with the macrophage phase (fig. 12) as well as the polymorphonuclear phase (fig. 8). During the course of the absorption, the macrophages invaded the plies of the catgut and caused irregular areas of absorption from within the strand as well as about the periphery (figs. 9, 10, 11, 12 and 13). The catgut was gradually broken up into smaller and smaller fragments as the absorption progressed (fig. 13). The length of time required for complete absorption of chromic catgut by this macrophage mechanism was three to six months or sometimes longer (fig. 14). In some instances, however, the absorption was apparently completed within three weeks to three months, probably because of an appreciable preliminary action by the leukocytes. Foreign body giant cells were often seen, and (figs. 12 and 14) occasionally one was able to detect a minute fragment of chromic catgut in the giant cell (fig. 14).

The most conspicuous observation made was that during the course of the relatively slow absorption the phagocytic cells took on the color characteristic of the chromic catgut. Dense clusters of these chromic-stained macrophages persisted in the location of the chromic catgut implant for long periods of time (fig. 14) after the catgut was actually absorbed and simulated the gross appearance of an unabsorbed fragment of chromic catgut (figs. 1, 3 and 6). This was observed as late as two years in fresh tissue specimens removed at autopsy or operation as well as in the fixed or cleared specimens.

When chromic catgut remained intact for ten days or more in the tissues, it was usually found to be surrounded by a thin fibrous tissue capsule. This was distinctly noticeable when the gross specimens were dissected at autopsy. The skin and the subcutaneous tissue were usually easily separated from the underlying muscular fascia without actually exposing the catgut knots or the free ends of the catgut beyond the knots. This was possible because this thin fibrous capsule sealed off the catgut exposed on the anterior rectus sheath from the overlying loose subcutaneous tissue. Instances in which the more slowly absorbed varieties of chromic catgut underwent relatively rapid absorption appeared to coincide with failure or delay in this encapsulation process. This gross evidence of fibroblastic response was supplemented also by microscopic observations (figs. 9, 10, 11 and 12).

The behavior of the catgut knot during the course of absorption was interesting from several standpoints. During rapid absorption by the leukocytic mechanism, the knot was generally the last part of the suture

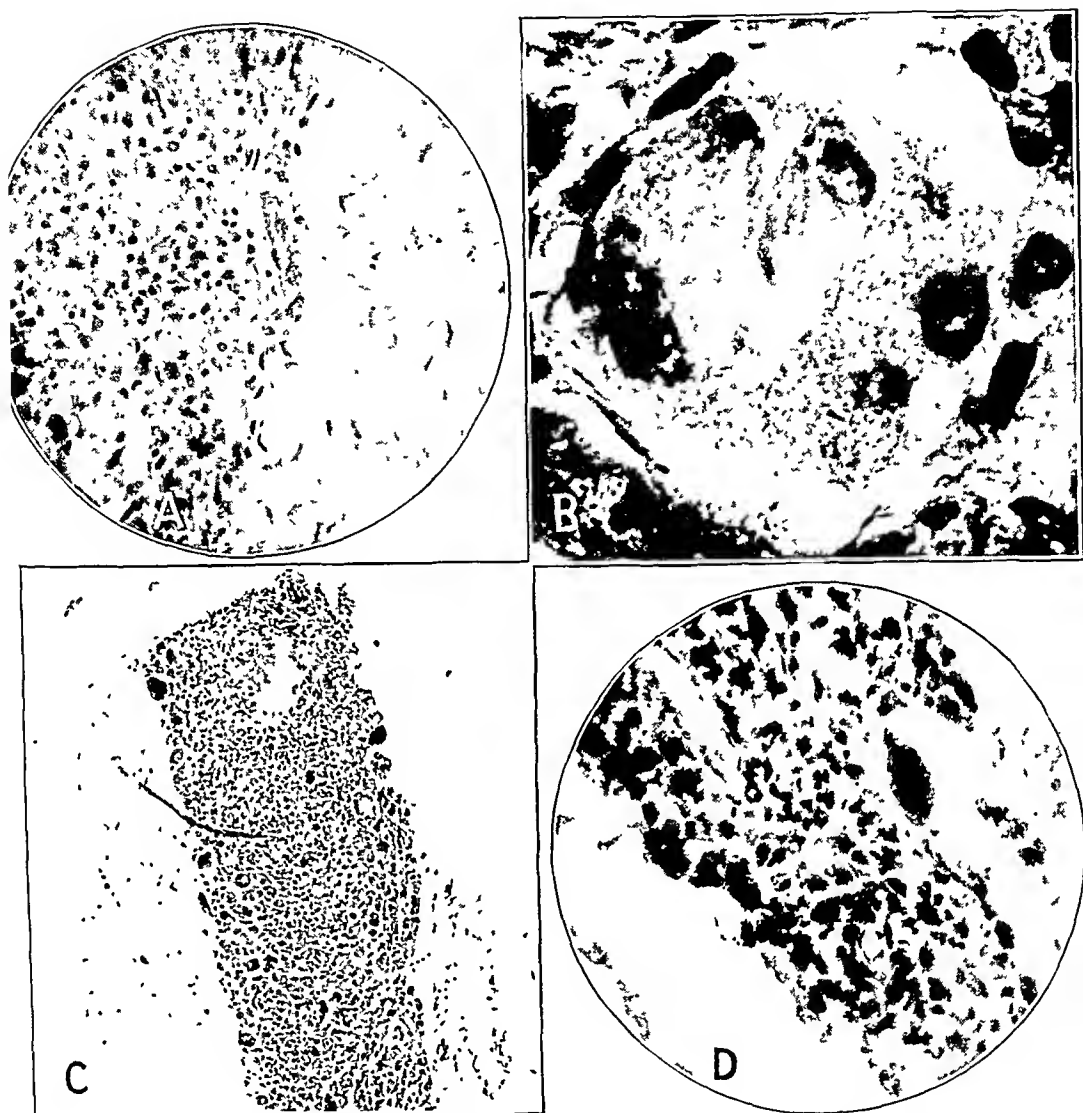


Fig. 14.—Photomicrographs showing the macrophage reaction which persists at the location of the chromic catgut for long periods after the catgut has been absorbed. These dense clusters of macrophages gave a gross appearance which simulated the appearance of an unabsorbed fragment of chromic catgut. No evidence of catgut could be found microscopically, and it appears that the macrophages have taken on the color of the chromic catgut which was absorbed by the macrophages. Occasionally one can detect a minute fragment of chromic catgut within a giant cell; however, this was not observed frequently enough to account for the strain in the tissues which resembled unabsorbed chromic catgut. *A* (six months), macrophage cluster but no evidence of chromic catgut. *B* (thirteen months), large multinucleated giant cell with fragment of chromic catgut engulfed. *C* (seventeen months), macrophages and numerous giant cells. *D* (twenty-seven months), macrophages and occasional giant cells.



to be absorbed (fig. 2). During slow absorption, the knot as a rule underwent absorption at a rate which was more nearly like that of the rest of the suture (figs. 1 and 3). In some specimens, it appeared that the triple throw square knots used for the implants underwent spontaneous untying in the absence of any appreciable evidence of absorption of the catgut (fig. 3). In these experimental implant series there was noticed no tendency to form draining sinuses from the catgut implant to the skin surface.

In certain products, it was not unusual to observe that the plies of the catgut tended to separate rather widely, although there may have been no gross evidence of absorption at that time (fig. 2).

#### COMMENT

When the slowly or intermediately absorbed type of catgut underwent relatively rapid absorption, this may have been due to several factors. The resistance of the catgut to digestion may have been appreciably less than that of other strands of the same size, type or brand. The tissues in which the catgut was implanted may have responded to the foreign substance with somewhat more exudative reaction than usual; this impaired the fibroblastic encapsulation process which apparently protects the catgut from the leukocytic mechanism of rapid absorption. The presence of some irritating factor of a chemical nature could contribute to such exudative reactions as may occur from time to time.

In the study of pepsin digestion tests, it was pointed out that the chromic catgut of one company appeared to show a somewhat different relation between pepsin digestion and duration of tensile strength in the tissues from that of most other companies. It is rather interesting to point out that this corresponded with the product which appeared from the microscopic studies to have caused a relatively conspicuous acute tissue reaction. It is probable that this more acute tissue reaction, consisting mainly of polymorphonuclear leukocytes, contributed to a more rapid rate of absorption than the degree of resistance of the chromic catgut would appear to warrant in view of the fact that comparable degrees of resistance in other products usually resulted in a slower rate of absorption with considerably less tissue reaction.

The relative differences in the rate of absorption of the various sizes, types and brands of surgical gut corresponded in general with those observed in the previously reported work. However, the duration of tensile strength was not necessarily directly proportional to the time required for complete absorption. The catgut which maintained its tensile strength for less than ten days was usually completely absorbed within a relatively short time after the loss of tensile strength. The catgut which remained intact beyond ten days usually required a long

time for complete absorption. It is not generally realized that the ultimate absorption of the latter type of catgut may require three to six months or sometimes longer. The descriptive literature put out by some of the manufacturers of surgical gut has included statements which do not appear to be confirmed in this work. For example, the twenty day chromic catgut of one manufacturer was stated to maintain its tensile strength for "approximately" twenty days in the tissues and to undergo complete absorption in three additional days. Statements such as this have led to an impression that the normal time required for complete absorption was a matter of several days after the loss of tensile strength instead of the several months observed for a considerable proportion of the twenty day or forty day chromic catgut studied in this work. It may be recalled also that in the observations on the duration of tensile strength in the tissues, it was rather unusual to have twenty day or forty day chromic catgut maintain its tensile strength for a period which would be considered an "approximation" of the absorption time specified on the label.

The behavior of the various sorts of surgical gut in the tissues was apparently related to the fundamental mechanism of absorption. There was on the one hand a polymorphonuclear leukocytic activity associated with rapid absorption, while on the other hand a macrophage activity was associated with slow absorption. In some instances, both types of cellular activity appeared to play a role in what appeared to be intermediate absorption.

There was a considerable difference in the manner in which the cellular response subsided following the completion of absorption. The leukocytic response subsided fairly promptly after rapid absorption. The macrophage response associated with slow absorption or intermediate absorption persisted for long periods after the catgut was actually absorbed (fig. 14).

A point of particular interest was the chromic-colored stain imparted to the protoplasm of the macrophages or histiocytes which participated in the absorption of the chromic catgut. The ability of macrophages or histiocytes to take up various types of vital-staining material in their protoplasm has been generally recognized. However, attention has not been conspicuously drawn to the apparent vital staining of macrophages or histiocytes which have been responsible for the absorption of chromic catgut.

It is probable that most instances in which surgeons have found what appeared to be unabsorbed chromic catgut in a healed incision which was reopened at a secondary operation nine months to two years later can be explained on the basis of persistent clusters of chromic-

stained macrophages.<sup>6</sup> It is exceedingly difficult to distinguish grossly between clusters of chromic-stained macrophages and unabsorbed chromic catgut without a microscopic section.

The character of the cellular response to foreign substances is generally indicative of the absence or the presence of irritating qualities in the foreign substance. Because of the striking differences often observed in the type and the magnitude of cellular response to various sorts of catgut, there are reasonable grounds for presuming that this may represent differences in the extent to which catgut acts as an irritant to the tissues. In view of the frequent observation that most types of chromic catgut were absorbed by a cellular mechanism usually characteristic of relatively nonirritating substances, it is possible that this indicated a nonirritating suture material. The leukocytic response characteristic of plain catgut and certain types of chromic catgut may have indicated an irritating suture material.

Just what contributes to the magnitude or the lack of irritation may differ in various instances. There appeared to be some relation between the resistance of the catgut to digestion as determined by the acid-pepsin digestion test and the magnitude of irritation observed, since the degree of resistance to digestion was generally inversely proportional to the amount of irritation observed. The chromicizing of catgut by the more modern commercial methods beyond some critical point appeared to result in a suture which usually caused less irritation to the tissues than untreated plain catgut. There was no apparent evidence that modern methods of chromicizing superimposed any additional irritating qualities on untreated plain catgut. The extent of chromicizing which accomplished this decreased irritation probably varied. Some methods of chromicizing, which may still be in use, did not appear to accomplish a lessened degree of original irritation, although subsequent to the alleviation of such irritation as originally existed, there was usually a long period of nonirritating and slow or intermediate absorption. Although the relatively resistant chromic catgut, which presumably represented fairly extensive degrees of chromicizing was usually slowly absorbed, this was not necessarily consistently observed. Whether the occasional evidence of irritation and rapid absorption was due to the local conditions of the tissues in which the catgut was implanted or to the presence of an extraneous irritating factor can only be surmised.

Bates<sup>3</sup> also observed that chromic catgut caused less reaction in the tissues than plain catgut. He attributed this to the fact that plain catgut

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6. One brand of tanned iodized catgut which has not been available on the market because it was made only to meet the needs of a certain situation was found to be intact as late as three years (Rhoads, J. E.; Hottenstein, H. F., and Hudson, I. F.: *The Decline in the Strength of Catgut After Exposure to Living Tissues*, Arch. Surg. **34**:377 [March] 1937).

was irritating to the tissues. He found also that the smaller sizes of chromic catgut caused less tissue reaction than the larger sizes and that the smaller sizes remained intact for a longer period than the larger sizes. His observations, however, were limited to the product of one company.

On the other hand, in their work in 1930, Howes and Harvey<sup>7</sup> found that chromic catgut caused a more intense polymorphonuclear and lymphocytic reaction than plain catgut. They observed the proliferation of fibroblasts at the periphery of the chromic catgut after five or six days. The twenty day chromic catgut which they studied at that time was found to undergo complete absorption in nineteen to twenty-three days.

Bower, Burns and Mangle<sup>4</sup> carried out studies on a product which demonstrated the relatively slight tissue reaction of very fine chromic catgut (size no. 00000) as compared with relatively small size chromic catgut (no. 0). It is of interest to note that it is not necessary to resort to such a fine size of chromic catgut as was used in the experiments of these authors to obtain relatively slight tissue reaction with most chromic catgut products. Further, no. 0 chromic catgut of most companies as well as the product which Bowers, Burns and Mangle studied was generally found to be in a better state of preservation at the end of ten days or more than was reported in their work.

Meade and Ochsner,<sup>8</sup> in their study of the relative value of catgut, silk, linen and cotton, found that catgut caused more tissue reaction than the other types of suture material. However, in reviewing the photomicrographs of the cotton, the linen and the silk in their articles in the light of observations made on most of the chromic catgut in our study of suture material, it appears that chromic catgut of certain types does not compare as unfavorably with nonabsorbable suture material from the standpoint of tissue reaction as they were inclined to conclude.

In the work of Bellas and Collins,<sup>9</sup> the tissue reaction of catgut, silk and a new nonreacting, noncapillary suture, known as plastigut, in which the essential components are synthetic plastics (polymerized condensation products of aliphatic and aromatic alcohols with short chain aliphatic aldehydes) was studied. They were impressed with the relatively nonreacting properties of plastigut as compared with catgut

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7. Howes, E. L., and Harvey, S. C.: Tissue Response to Catgut Absorption, Silk, and Wound Healing, *Internat. J. Med. & Surg.* **43**:225, 1930.

8. Meade, W. H., and Ochsner, A.: The Relative Value of Catgut, Silk, Linen and Cotton as Suture Materials, *Surgery* **7**:485, 1940.

9. Bellas, J. E.: Suture Studies: A New Suture, *Arch. Surg.* **41**:1414 (Dec.) 1940. Collins, C. U., and Bellas, J. E.: The Influence of Sutures on Operative Wounds, *Tr. West. S. A.* (1938) **48**:316, 1939.

or even silk. However, their observations on catgut did not apparently include examples of relatively nonreacting chromic catgut such as those found in our work.

Several factors may influence the amount of irritation in the tissues other than such properties as are inherent in untreated surgical gut. Irritating chemicals used in the chromicizing process or unfixed or unstable chromic compounds resulting from the chromicizing process which have not been thoroughly removed from the catgut could possibly explain some of the instances of apparent irritation. The xylene or toluene which has been used as a tubing fluid for boilable catgut is insoluble in water and is difficult to remove completely from the catgut except by thorough washing in alcohol. The presence of xylene or toluene in relatively small amounts in the catgut when it is introduced into the tissues could account for appreciable irritation. The alcohol used in tubing fluid for nonboilable catgut could cause some irritation if it did not evaporate to a considerable extent before the catgut got into the tissues. The presence of chemicals in the tubing fluid designed to act as bactericidal agents also may contribute to tissue irritation. In addition there is some evidence that the alcoholic tubing fluid of some varieties of nonboilable catgut contains appreciable amounts of a liquid which is insoluble in water and which may be the source of irritation if it is carried into the tissues along with the catgut. Further studies on the tubing fluids commonly used will be the subject of a subsequent communication.

In an endeavor to eliminate any possibility of irritation from the tubing fluid or chemical agents therein, it appears logical to consider using surgical gut which has been sealed up in dry tubes after the heat-sterilizing process. When the tube is opened, the dry catgut can be moistened with physiologic solution of sodium chloride to permit whatever flexibility is desired.

Aside from any considerations of the nature of the suture material, the bulk of the suture material involved may appear to contribute to the problem of irritation in the tissues. Although silk is considered to be nonirritating to the tissues, it is generally agreed that the use of large sizes of silk is not desirable for buried sutures because of the incidence of draining sinuses which will occur even in clean wounds. These draining sinuses may be considered evidence of irritation from some points of view, although the fundamental nature of silk is essentially nonirritating in character. The draining sinus represents a failure on the part of the tissues to encapsulate and incorporate the silk because of the bulk involved. In those instances in which the tissue tolerance for a given bulk of fundamentally nonirritating foreign material is

exceeded, one may then expect to find what appears to be evidence of irritation. This is really a matter of the size of the suture material used, rather than of any irritating quality of the suture material.

When draining sinuses develop after the use of large sizes of catgut, it is often attributed to irritating qualities of the catgut, although this explanation may not necessarily be applicable in the light of observations made in this work. The mechanism involved in the formation of draining sinuses from catgut does not appear to differ essentially from that involved in the formation of them from silk, because the type of catgut which is likely to cause a draining sinus is the slowly absorbed, relatively resistant and nonirritating chromic catgut of the larger sizes. The important aspect is that when the bulk of suture material which the tissues will tolerate at any focal point has been exceeded, the draining sinus will develop regardless of whether silk or this variety of catgut is used. The draining sinus represents a failure of the fibroblastic mechanism to encapsulate the foreign material. Although the bulk involved is generally the most important factor in determining the adequacy of the fibroblastic mechanism, other factors, such as bacterial contamination of the wound, unusually large amounts of plain catgut for ligatures, irritating substances from the tubing fluid introduced into the tissues with the catgut or an impaired fibroblastic response of the tissues due to vitamin or nutritional disturbances, may be of significance. It is of interest to note that the type of catgut which causes the most noticeable irritation, as evidenced by the acuity of the tissue reaction, is usually the rapidly absorbed variety of catgut. This kind of catgut would not be present in the tissues long enough to cause a draining sinus.

In view of the fact that some of the so-called twenty day chromic catgut which has been studied was found in advanced stages of absorption in various experimental implant specimens within six to ten days, it is not surprising that surgeons report from time to time that they could find only a few shreds of the chromic catgut which they had used to suture the abdominal wound and which they had an opportunity to examine again in six to ten days because of disruption. It is not necessary to assume an abnormal or premature absorption of the chromic catgut due to peculiarities of the patient's tissues in cases such as this because the rapid rate of absorption may be characteristic for that particular variety of catgut. One can ascertain whether a lot of chromic catgut is of the rapidly absorbed variety by clinical tests, such as the tension suture test or seton test previously described.<sup>5</sup> Also, one can determine whether the digestion time in acid-pepsin solution is more within the range generally found for plain catgut or is substantially more

resistant to digestion than plain catgut.<sup>2</sup> This will give fairly reliable indirect evidence as to whether any particular catgut is of the rapidly absorbed variety.

Not to be overlooked in this study of suture material is the possibility of allergic reactions playing a role in the rate of absorption of the suture materials as well as in the tissue reaction incited. The work of Kraissl, Kesten and Cimiotti,<sup>10</sup> as well as that of Langston<sup>11</sup> and Farris<sup>12</sup> and other workers, must be taken into consideration. In the experimental animals studied in our work there was little likelihood of sensitization to catgut because many of these animals had not had any previous operations. However, the presence of Forssman antibodies of high titer in some of the animals might have been responsible for some differences in tissue reactions. Because of the relative uniformity of reaction incited by the various suture materials in a large series of animals, it is unlikely that allergic phenomena contributed substantially to the tissue reactions described in our work. Pickrell<sup>13</sup> concluded that catgut does not act as an antigen to induce the hypersensitive state.

#### RECOMMENDATIONS

It is probable that the larger sizes of surgical gut, which are designed for closure of fascial layers of relatively healthy patients by the average surgeon, should have properties comparable to those of what has been described as intermediately absorbed catgut, i. e., about ten days' duration of tensile strength and complete absorption in approximately three weeks to three months. This recommendation is based on an analysis of the situation from several points of view:

1. The minimum time required for the healing of a normal clean wound should be considered approximately ten days. Howes, Sooy and Harvey<sup>14</sup> found that most of the strength of the healing wound was obtained in ten days, although fourteen days was required for maximum strength. Chouke and Whitehead<sup>15</sup> found good healing in eleven days and apparently complete repair after sixteen days.

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10. Kraissl, C. J.; Kesten, B. M., and Cimiotti, J. G.: The Relation of Catgut Sensitivity to Wound Healing, *Surg., Gynec. & Obst.* **66**:628, 1938.

11. Langston, H. T.: The Problem of Catgut Sensitivity and Its Relationship to Wound Healing, *Ann. Surg.* **113**:1117, 1941.

12. Farris, J. M.: Tissue Reactions to Suture Materials, *Ann. Surg.* **114**:1128, 1941.

13. Pickrell, K. L.: Studies on Hypersensitivity to Catgut as a Factor in Wound Disruption, *Bull. Johns Hopkins Hosp.* **64**:195, 1939.

14. Howes, E. L.; Sooy, J. W., and Harvey, S. C.: The Healing of Wounds as Determined by Their Tensile Strength, *J. A. M. A.* **92**:42 (Jan. 5) 1929.

15. Chouke, K. S., and Whitehead, R. W.: Wound Healing, *Surgery* **9**:194, 1941.

2. If one uses surgical gut which is completely absorbed in less than three weeks, the duration of tensile strength will probably be no longer than five to eight days. This rapidly absorbed type of suture material does not have an adequate duration of holding power in the tissues to insure a safe period of healing for the fascial layers.

3. If one uses surgical gut of the slowly absorbed variety in the larger sizes, one may obtain a considerably longer duration of tensile strength. However, one is likely to encounter draining sinuses from time to time because the bulk of relatively resistant suture material may exceed the tolerance of the tissues for foreign substances of a nonirritating quality.

4. The intermediately absorbed type of suture material offers those who prefer to use the larger sizes of catgut an opportunity to have a reasonably safe duration of holding power of the suture, at least for the average run of reasonably healthy surgical patients. This duration of tensile strength will probably not be adequate for debilitated patients or those who might be expected to have some appreciable delay in wound healing because of vitamin C deficiency or hypoproteinemia. The use of this intermediate type of suture material in the larger sizes does not eliminate the possibility of an occasional draining sinus; however, the incidence of this condition should be expected to be appreciably less than when one uses the larger sizes of slowly absorbed chromic catgut.

The practical application of this study of the absorption of surgical gut from the standpoint of clinical surgery revolves about minimizing the bulk of suture material concentrated at any one point in the operative wound. The logical answer to the problem of wound closure with catgut is the use of the smaller sizes (no. 0, no. 00 and no. 000) of slowly absorbed chromic catgut for suturing fascial layers such as the anterior rectus sheath or the midline fascia (interrupted technic). This will give a maximum duration of holding power of the absorbable type of suture material (with preferably fifteen to twenty-five days' duration of tensile strength) without undue difficulties from draining sinuses because of the relatively small bulk of suture material involved at any one point in the wound.

Because of the relatively acute tissue reaction generally associated with plain catgut, it seems desirable to minimize the total bulk of this rapidly absorbable suture material. The tissues will tolerate moderate amounts of the smaller sizes, especially the no. 00 and no. 000 sizes, without appreciable clinical evidence of reaction or exudation. Considerable amounts of the larger sizes (no. 2 and no. 1) of plain catgut may contribute to the reaction and the exudation which are generally described as "characteristic of catgut wounds" by those who advocate nonabsorbable suture material. It is relatively infrequent that a situation is encountered which requires a plain catgut of greater tensile strength



for ligatures in the superficial tissues than is afforded by a no. 00 size (7 pounds [3.2 Kg.]) or at most a no. 0 size (10 pounds [4.5 Kg.]).

In a clinical trial of fine chromic catgut of the slowly absorbed type for ligatures (no. 000) in the superficial tissues, it was not found entirely satisfactory because it was occasionally necessary to remove fragments, usually knots, of the chromic catgut at somewhat later dates. If one has occasion to ligate a vessel of appreciable size in the superficial tissues, however, it is safer to use fine chromic catgut than fine plain catgut. The latter may become so softened by the tissue fluids that it may untie spontaneously before the vessel becomes securely occluded from an organized clot. Taylor<sup>16</sup> found that plain catgut which has been moistened is not a satisfactory material with which to obtain a secure knot as compared with other types of suture material, regardless of the type of knot used. Ligatures of fine chromic catgut appear to be better tolerated in muscle or on muscular fascia than in the subcutaneous tissues.

Relatively fine chromic catgut offers a more reliable closure of the peritoneum than is afforded by larger sizes of plain catgut. Howes and Harvey<sup>17</sup> drew attention to the fallacy of using a suture which has a tensile strength far in excess of the holding power of the tissues in which it is inserted. Their extensive work on suture material and wound healing brought out the importance of the surgical principle of using smaller sizes of catgut for wound closure. Their recommendations for the size of suture and ligature material based on their work have been largely responsible for the wider use of the smaller sizes of catgut. The recommendations presented by us in the preceding paragraphs regarding the selection of the smaller sizes of catgut for interrupted technic are essentially a reflection of their views on the subject, supported and extended by data derived from our own study.

One is hesitant, however, to make any specific suggestions which might lead to the use of suture material with which the user is unaccustomed until such time as the various manufacturers are somewhat more in accord regarding the absorptive qualities of the various sizes and types of chromic catgut. The use of the smaller sizes (no. 0, no. 00 and no. 000) of chromic catgut from some sources could lead to serious consequences if it should prove to be a product which is more rapidly absorbed in the smaller sizes. Nevertheless, the fundamental points

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16. Taylor, F. W.: *Surgical Knots*, *Ann. Surg.* **107**:458, 1938; *Surgical Knots and Sutures*, *Surgery* **5**:498, 1939.

17. Howes, E. L.: *The Immediate Strength of the Sutured Wound*, *Surgery* **7**:24, 1940. Howes, E. L., and Harvey, S. C.: *The Strength of the Healing Wound in Relation to the Holding Strength of the Catgut Suture*, *New England J. Med.* **200**:1285, 1929. Howes, E. L.: *How to Use Catgut*, *Surg., Gynec. & Obst.* **73**:319, 1941.

derived from this study of the absorption of surgical gut lead one to recommend the use of the smaller sizes of catgut if properly labeled regarding their absorptive qualities.

#### SUMMARY

Experimental and clinical observations were made on the absorption time in the tissues of approximately 2,000 or more catgut implants.

The relative rate of absorption of the various sizes, types and brands of surgical gut corresponded in general with previous observations on the duration of tensile strength in the tissues and the digestion time in acid-pepsin solution.

The length of time required for complete absorption after the loss of tensile strength was as follows: The catgut which usually lost its tensile strength in less than ten days was rapidly absorbed within one to three weeks. The catgut which usually maintained its tensile strength beyond ten days was generally slowly absorbed within three to six months. Catgut which remained intact for about ten days was often intermediately absorbed between three weeks and three months.

The mechanism of absorption presented certain fundamental differences in that a polymorphonuclear leukocytic activity was usually associated with rapid absorption, while a macrophage activity was generally the conspicuous aspect of slow absorption. A leukocytic response of varying magnitude was present as a preliminary phase of slow absorption; however, it was usually not conspicuous and did not appear to contribute noticeably to the absorption. In intermediate absorption, both types of cellular mechanisms probably contributed to the process of absorption.

Following rapid absorption by the leukocytic mechanism, the cellular response subsided promptly. However, after the completion of slow absorption or intermediate absorption, the macrophages or histiocytes often remained in the tissues for a long time.

The macrophages or histiocytes which participated in the absorption of chromic catgut appeared to take on the color characteristic of the particular catgut.

The presence of persistent clusters of chromic-stained macrophages or histiocytes in the tissues often simulated the gross appearance of unabsorbed chromic catgut.

Most varieties of chromic catgut elicited less tissue reaction of a leukocytic or exudative type than plain catgut.

#### CONCLUSIONS

The method of labeling surgical gut (catgut) which has recently been adopted as a result of the recommendations of the Committee for Revision of the United States Pharmacopeia is a substantial improve-

ment over that formerly used. The fallacy of designating a specific number of days as the absorption time, such as ten days, twenty days or forty days, has been clearly demonstrated.

Although the present adopted classification for labeling surgical gut recognizes four different types, it would appear from this work that there are probably not more than three general categories into which surgical gut can be reasonably classified on the basis of absorptive qualities.

There do not appear to be any major clinical problems in wound closure which cannot be reasonably well solved by absorbable suture material. Excessive tissue reaction, inadequate duration of holding power of the suture and foreign body reactions, as evidenced by draining sinuses, can be prevented to a considerable extent by the proper selection of suture material from the standpoint of size and absorptive qualities.

More uniform absorptive standards for the different types of surgical gut from the various manufacturers would be of considerable aid to the surgeon in selecting the absorbable suture material best suited to his needs.

Dr. William B. Steen, of Tucson, Ariz., gave many helpful suggestions during the preparation of this paper.

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# ESSENTIAL BIOCHEMICAL DERANGEMENTS IN HYPERTHYROIDISM

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Exhaustive efforts to find measurable abnormalities of the inorganic constituents, other than of iodine, in the blood of patients with hyperthyroidism have been fruitless. The literature on these endeavors was well summarized by Maddock, Pedersen and Coller<sup>1</sup> and by Bartels.<sup>2</sup> It is not sufficiently appreciated with what care the constancy of concentrations of the electrolytes, particularly of the cations, is maintained. Yet all who have particular interest in this field must have felt the urgency of the belief that something measurable by biochemical methods must be importantly disturbed in patients with thyrotoxicosis and have wished, to quote Maddock, "we only knew what to measure." It is my contention that investigators have been analyzing the wrong body fluid, as will presently be shown.

## SERIAL DETERMINATIONS OF THE CARBON DIOXIDE-COMBINING POWER OF PLASMA

My own interest in the acid-base equilibrium of the patient with hyperthyroidism was aroused in 1930 in connection with my development of the breath-holding test.<sup>3</sup> The work of Gesell<sup>4</sup> indicated that the  $p_H$  of the respiratory center was the final factor in determining the breaking point, beyond which voluntary apnea was not possible and that tissue acidosis, by whatever means produced, reduced the ability to hold the breath. There was little evidence bearing on the possibility that there might be an acidosis in thyrotoxicosis, for the English and American literature on the subject apparently started and stopped with single observations on the carbon dioxide-combining power of the

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1. Maddock, W. G.; Pedersen, S., and Coller, F. A.: Studies of Blood Chemistry in Thyroid Crisis, *J. A. M. A.* **109**:2130 (Dec. 25) 1937.

2. Bartels, E. C.; Stuart, C. K., and Johnson, E. C.: *Tr. Am. A. Study Goiter*, 1940, p. 133.

3. Bartlett, W., Jr.: *Surg., Gynec. & Obst.* **63**:576, 1936.

4. Gesell, A., cited by Bartlett, W., Jr.: *Tr. Am. A. Study Goiter*, 1930, p. 129.

TABLE 1.—Basal Metabolic Rate and Carbon Dioxide-Combining Power of the Plasma Before and After Thyroidectomy

Patient	Age	Sex	Disease	Patient Unstabilized		Before Operation		After Operation	
				Basal Metabolic Rate	Carbon Dioxide-Combining Power of Plasma, Vol-umes per Cent	Basal Metabolic Rate	Carbon Dioxide-Combining Power of Plasma, Vol-umes per Cent	Basal Metabolic Rate	Carbon Dioxide-Combining Power of Plasma, Vol-umes per Cent
1	30	M	Exophthalmic goiter.....	+91*	50	+32*	60	+4	64†
2	50	F	Exophthalmic goiter.....	+75 (?)	56	.....	..	+10	50
3	22	M	Exophthalmic goiter.....	+70 (?)	61	+16	60	+11	59‡
4	39	F	Exophthalmic goiter.....	+10	55	+37	53‡	+7	53
5	42	F	Exophthalmic goiter.....	+50 (?)*	51	+12	52‡	+21	59
6	44	F	Exophthalmic goiter.....	.....	..	+31*	51	+10*	53‡
7	23	F	Exophthalmic goiter.....	+26	53	+11	62	—4	63‡
8	29	M	Exophthalmic goiter.....	+64	60	+23	61	+19	60‡
9	37	F	Exophthalmic goiter.....	.....	..	+16	57	+5	60‡
10	59	F	Toxic adenoma.....	+32	72	+11	68	+15 (?)	71
11	38	F	Toxic adenoma.....	.....	..	+22	61	—15	57
12	48	F	Toxic adenoma.....	.....	..	+25	62	—9	67
13	36	F	Toxic adenoma.....	+45	57	.....	..	+2	67
14	27	F	Toxic adenoma.....	.....	..	+3	61	0	59
15	52	F	Toxic adenoma.....	.....	..	+31	59	+16	58

\* Auricular fibrillation.

† Vena puncture difficult.

‡ Two stage thyroidectomy.

arterial plasma of 6 patients by Davies, Meakins and Sands<sup>5</sup> in 1924. These authors reported values falling within normal limits. A few reports<sup>6</sup> were found in the foreign literature, but there was decided conflict in the results, serial studies during the course of treatment were few, and complicated cases were frequently included. Accordingly, between 1933 and 1935, I made serial determinations of the carbon dioxide-combining power of the venous plasma of 15 patients with thyrotoxicosis and have since added results obtained in 3 additional cases. Observations were made on the patient (1) when unstabilized (usually untreated), (2) when well stabilized and ready for operation and (3) on the fifth to the seventh postoperative day. I did not find values outside the range of normal in any of these determinations or in numerous other single determinations, including one on a patient in spontaneous crisis. On the other hand, it seemed of possible significance that in 8 of these 18 cases, a measurable rise in alkali reserve was observed with clinical improvement and that the sickest patients showed values at the lower limits of normal. Among the remaining patients, no variation beyond the limit of error of the method was observed, except for 1 patient, who showed a small drop in alkali reserve after operation. These data are recorded in table 1.

#### RESPONSE OF THE CIRCULATION TO MEASURED EXERTION

In the course of these studies, I became interested in the response of the circulation to measured exertion and have reported elsewhere<sup>7</sup> the value of the estimation of the pulse rate and the pulse pressure in the differentiation of mild hyperthyroidism from conditions simulating it. Moreover, the carbon dioxide-combining power of the plasma in the patient with thyrotoxicosis falls sharply after brief light exertion and is slow to return to resting values, while it shows little or no measurable drop after similar exertion in a normal person. It seemed clear, therefore, that the patient with thyrotoxicosis maintained a normal alkali reserve when at rest but that a decided diminution into the range of acidosis developed on exertion. The reasons for this and the possible biochemical derangements accompanying it were not yet clear, and I was not hopeful of finding them in the blood by existing technics. Nor

5. Davies, H. W.; Meakins, J., and Sands, J.: *Heart* **11**:299, 1924.

6. Walinski, F., and Herzfeld, E.: *München. med. Wchnschr.* **73**:2153, 1926. Damble, K., and Reuter, A.: *Arch. f. klin. Med.* **125**:690, 1933. Coelho, E.: *Endokrinologie* **10**:74, 1932. Altenburger, E., and Boger, A.: *Klin. Wchnschr.* **12**:1983, 1933. Skold, E.: *Arch. f. klin. Chir.* **151**:600, 1928. Zondek, H.: *Deutsche med. Wchnschr.* **55**:345, 1929. Koenig, W.: *Arch. f. klin. Chir.* **164**:213, 1931.

7. Bartlett, W., Jr.: *Endocrinology* **22**:543, 1938; *J. Mississippi Valley M. Soc.* **63**:96, 1941.

TABLE 2.—*Total Titratable Acid of the Urine in Hyperthyroidism*

Patient	Age	Sex	Patient Unstabilized (Admitted)			Before Operation			After Operation (Patient Discharged)		
			Rate	Acid, Ce., Tenth Normal	Basal Metabolic Rate	Days	Acid, Ce., Tenth Normal	Basal Metabolic Rate	Days	Acid, Ce., Tenth Normal	Basal Metabolic Rate
1	52	F	4	270 (334-204)	+33	2	93 (126-50)	+20	3	85 (122-62)	
2	44	F	..	.....	....	5	237 (259-153)	+18	3	251 (291-209)	+19
3	48	F	1	180	+33	4	61 (84-46)	+17	4	18 (51-0)	+10
4	29	F	7	316 (425-237)	+41	3	217 (253-233)	+15	3	128 (136-111)	+4
5	50	F	7	270 (326-207)	+29	3	103 (273-153)	+21			
						3	155 (258-111)	+11	4	126 (163-68)	+4
6	32	F	..	.....	....	..	.....	+38	5	195 (219-142)	+12
									3	92 (90-94)	
7	17	F	6	382 (455-294)	+38	..	.....	....	5	130 (204-73)	+5
8	60	F	3	314 (348-262)	+30	6	197 (252-100)	+31	5	227 (429-185)	
									4	220 (238-177)	+19
9	19	F	5	357 (388-315)	+50	10	135 (193-80)	+24			
								+16	6	96 (147-65)	-13

did the developing interest in impairment of liver function in thyrotoxicosis throw immediate light on this question of fundamental importance.

#### URINARY EXCRETION OF ACIDS IN HYPERTHYROIDISM

An investigation of the urine seemed to offer more promise than that of any other body fluid, and I recently presented a detailed summary of my findings.<sup>8</sup> At the suggestion of Somogyi, I have studied the total titratable acid of the urine in some 15 hospitalized patients who were given diets, constant, in each case, in the quantities of basic and acid-forming components and in total daily caloric intake. These diets were maintained throughout the preoperative period of hospitalization and were ordinarily resumed on the third or fourth postoperative day. After a preliminary period of stabilization with the diet, daily collection of twenty-four hour urine under standard precautions was carried out and was resumed in the postoperative period until the patient's discharge from the hospital. The period of preoperative observation varied from five days to six weeks; the postoperative studies lasted from three to nine days after the resumption of the diet. The difficulties of maintaining such a regimen are not inconsiderable, but for 9 of the patients the data are complete enough to furnish dependable evidence, and excerpts from the protocols appear in table 2. The number of consecutive days selected in each period of observation, the average excretion of total titratable acid (expressed in terms of cubic centimeters of tenth-normal acid) for this number of days, together with the range of excreted acid during this period are given. Patients 5 to 9, inclusive, were operated on by a two stage procedure; hence data in the second line in each of these cases pertains to the second lobectomy. Physical activity of all patients during the period of observation was limited to getting from bed to chair and to the bathroom.

These results have been discussed at length elsewhere.<sup>8</sup> It is clear that a close relation exists between the clinical course of the patient and the excretion of total titratable acid in the urine. When the improvement has been pronounced in the preoperative period (patients 1, 3 and 9), the fall in quantity of excreted acid has been profound. When the basal metabolism has been promptly reduced postoperatively below admission observations (patients 3, 4, 5, 7 and 9), the last recorded quantities of acid excreted before discharge from the hospital are only one fourth to one seventh of the amounts excreted on admission. On the other hand, when a considerable fall in the basal metabolic rate is not obtained promptly after operation (patients 2 and 8), the postoperative excretion of acid is not importantly different from that of the

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8. Bartlett, W., Jr.: *Proc. Soc. Exper. Biol. & Med.* **45**:196, 1940.



immediately preoperative period, though it has fallen considerably from the amounts excreted on admission.

Patient 9 was followed in more detail over a period of some eight weeks, during which she experienced several minor exacerbations while in a relatively refractory phase of the disease. During such exacerbations, the constituents of her urine under study would vary in characteristic ways, as indicated in table 3 (under the dates of January 27 and 28), in that the total acid, the organic acid and the ammonia would rise and the  $p_{H}$  would fall. I regard the rise of urinary ammonia as an expression of an effort to conserve fixed base under stress. By contrast, the fall in the titrated components and the rise in  $p_{H}$  following the completion of the two stage thyroidectomy was striking. Comparison of the postoperative values for total titratable acid with the

TABLE 3.—*Urinary Findings in Case 9*

	Before Operation				Operation		After Operation			
	1/25	1/26	1/27	1/28	2/7	2/29	3/6	3/7	3/8	3/9
Date.....										
Volume.....	2,100	1,500	2,100	2,650			3,100	2,750	2,350	2,740
Total acid *.....	142	102	172	190			99	99	65	65
Organic acid †.....	26.8	14.4	20.1	33.9			35.9	26.4	26.3	21.9
Ammonia nitrogen ‡.....	0.239	0.211	0.281	0.439			0.658	0.481	0.439	0.446
$p_{H}$ .....	6.0	6.0	5.8	5.8			6.5	6.5	...	7.0
Basal metabolic rate.....	...	...	...	+32			...	...	...	-13

\* Tenth normal, cc. per 24 hours.

† Milliequivalents per 24 hours.

‡ Gm. per 24 hours.

quantities excreted on admission (table 2) some ten weeks previously indicates the great change that had taken place.

I have not identified the organic acids the excretion of which varies in the same direction as that of the total titratable acid, but my assumption is that they are ketone acids. The tendency of patients with thyrotoxicosis in postoperative reactions to ketosis seems to be generally known but is not often commented on. Of great significance, I believe, was the recent demonstration by Somogyi<sup>9</sup> of large quantities of ketone acids in the blood of certain patients with hyperthyroidism. In 3 of my own cases, serial determinations of the carbon dioxide-combining power of the plasma showed a rise in alkali reserve coincident with a fall of total titratable urinary acid in 2 cases but insignificant changes in alkali reserve when only a small decrease in urinary acid excretion occurred in the third case. Whether this correlation will be maintained in a significant number of cases remains to be seen.

9. Somogyi, M.: Personal communication to the author.

## COMMENT

The significance of these observations on the mechanisms for maintenance of acid-base equilibrium extends beyond the mere demonstration of a state of acidosis, more or less well compensated, as characteristic of thyrotoxicosis and varying with the severity of the disease. I believe that they have an important bearing on the manner in which the tissues take up and release water (and electrolytes). This point has been discussed briefly in a previous paper,<sup>10</sup> in which the hydration of the patient with hyperthyroidism was reviewed. I pointed out that all the known derangements of metabolism in thyrotoxicosis worked toward the retention of water by the tissues in the exacerbations seen spontaneously and after operation ("crisis in miniature"). The occurrence of cerebral and pulmonary edema as characteristic events of crisis, even in patients who showed obvious dehydration, was stressed, and the demonstration by Collier and Maddock<sup>11</sup> of actual gain in weight with fall of insensible perspiration in the period of rising temperature after operation was emphasized. I believe that this has not been given the attention it deserves, for the common clinical practice has been to give large quantities of fluids, often directly into the circulation, at a time when the tissues are already unable properly to handle water. I therefore urged that fluids be restricted in such situations and that hypertonic dextrose be given intravenously to combat the tendency to water retention and to guard against ketosis. The evidence brought forward by Bartels<sup>12</sup> and Brown and McCray<sup>13</sup> of a reduction in plasma proteins in hyperthyroidism was not sufficiently emphasized as an important indication that the patient cannot be properly hydrated until the plasma proteins have been restored to normal. My own unpublished data substantiate these findings and indicate further that a reversal of the albumin-globulin ratio is a common occurrence in the immediately postoperative phase. Pending increase in the colloid osmotic pressure of the blood by transfusion of plasma or of whole blood or by the administration of acacia, limitation of fluids and the use of hypertonic electrolytes intravenously offer an alternative method of preventing serious and often fatal water-logging of the tissues, especially of the brain and the lungs. The therapeutic use of oxygen in high concentration aids, of course, in the delivery of oxygen to the tissues at higher tension and makes easier the more complete oxidation of ketone bodies, helps to maintain capillary integrity and tends to interrupt the vicious cycle that is always set up between tissue edema and tissue anoxemia.

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10. Bartlett, W., Jr.: *Surg., Gynec. & Obst.* **71**:450, 1940.

11. Collier, F. A., and Maddock, W. G.: *Tr. Am. A. Study Goiter*, 1933, p. 188.

12. Bartels, E. C.: *New England J. Med.* **218**:289, 1938.

13. Brown, R. B., and McCray, P. M.: *Endocrinology* **22**:302, 1938.

I have the support of Elliot<sup>14</sup> in the view that the acidosis of hyperthyroidism damages the capillaries, increasing their permeability, and that this may be responsible to a large extent for the decrease of plasma protein, particularly of the albumin fraction, by permitting the passage of protein from the capillaries to the tissues, where it tends to hold water. That this acidosis may decrease also the production of serum albumin by the liver through damage to the hepatic capillaries is more truly a matter of speculation but seems as reasonable as any other hypothesis in the light of present knowledge. Certainly, the diet of the patient with thyrotoxicosis who is being prepared for operation should be high in caloric intake with relatively large amounts of carbohydrate, a liberal allowance of protein and a small fat content. This is a decided reversal of the earlier practice of trying to attain a large caloric intake by diets with high fat intake and the limitation of protein for fear the specific dynamic action of the latter would increase basal metabolism.

#### SUMMARY

The essential biochemical derangement of thyrotoxicosis is an acidosis which is probably attributable in part to ketosis. The carbon dioxide-combining power of the plasma is maintained within normal limits even in severe exacerbations so long as the patient is at rest and his physiologic needs for water and nourishment are met, but a prompt decrease in alkali reserve occurs on exertion. During improvement on treatment preliminary to thyroidectomy and subsequent to operation, a profound fall in the total titratable acid of the urine, of the organic acids and of ammonia occurs, and the  $p_H$  of the urine rises if the patient's intake of food is kept constant quantitatively and qualitatively. In nearly 50 per cent of the patients who show prompt improvement after thyroidectomy, a rise in the alkali reserve of the plasma occurs.

I believe that acidosis bears a fundamental relation, probably causative, to the tendency of the patient with hyperthyroidism to water retention by the tissues through impairment of capillary integrity. The relation of this process to the loss of plasma protein from the blood to the tissues to the possible interference with serum albumin production by the liver and to the establishment of a vicious cycle of tissue edema and cyanosis is discussed. Appropriate therapy is mentioned.

University Club Building.

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14. Elliot, J.: Personal communication to the author.

# CYSTADENOMA OF THE PANCREAS

## REPORT OF FIVE CASES

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NEW YORK

Five patients with cystadenoma of the pancreas have been treated in the surgical department of the New York Hospital during the past nine years, and it is with the purpose of bringing out certain diagnostic features and operative findings that the 5 cases are hereinafter reported and discussed.

No attempt has been made to review the literature on pancreatic cysts, for this was done recently by Kennard<sup>1</sup> in 1941. However, certain publications are of special interest in regard to the incidence and the classification of these tumors. White<sup>2</sup> found 3 cases of pancreatic cyst, 1 of which was hydatid, in 6,708 autopsies at Guy's Hospital in London, England; Young,<sup>3</sup> 5 patients with cysts between 1920 and 1937 at the Massachusetts General Hospital, Boston; and Judd,<sup>4</sup> 88 who came to operation among a total of 723,397 patients admitted to the Mayo Clinic, Rochester, Minn. In a series of 121 cases of pancreatic cyst, Oser<sup>5</sup> found an equal distribution between the sexes (60 male and 61 female), and Kennard<sup>1</sup> stated that the cysts commonly appear in middle life. Boyd<sup>6</sup> classified pancreatic cysts as retention cysts, congenital cysts, cystadenomas and pseudocysts.

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From the Department of Surgery, New York Hospital and Cornell University Medical College.

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4. Judd, E. S.; Matson, H., and Mahorner, H. R.: Pancreatic Cysts: Report of Forty-Seven Cases, *Arch. Surg.* 22:838-849 (May) 1931.

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The most recent of our cases (case 1) is presented in detail to emphasize certain features, while the other 4 cases are abstracted more briefly.

#### REPORT OF CASES

CASE 1.—M. J., a white American-born woman aged 37 years, was admitted to the New York Hospital on Aug. 2, 1941. Her chief complaint was severe pain in the left upper quadrant of the abdomen of four days' duration.

The past history was remarkable only in that the patient had toxemia of pregnancy in 1933; she was delivered of a healthy child.

Nine years before admission, the patient began to have attacks of pain in the epigastrium and the left upper quadrant of the abdomen associated with nausea and vomiting. The pain radiated to the left side and the back and was cramplike. Five years before admission, cholecystectomy for stones was done elsewhere. There was only partial relief of the pain, and she continued to have three or four attacks per year of gnawing, aching pain in the left upper quadrant of the abdomen. Four years before admission, a mass was noted in the upper part of the abdomen. One year later, she was admitted elsewhere with severe attacks of pain in the upper part of the abdomen, and operation was advised but refused. Mild diabetes was found at this time. During the year before admission, the diabetes increased in severity so that she lost 40 to 50 pounds (18.1 to 22.7 Kg.) and had polyuria and polydipsia. Her family physician prescribed 45 units of insulin a day and effected good control of the diabetes. Two months before admission, the patient had a severe attack of pain in the left upper quadrant of the abdomen; four days before entrance into the hospital, cramplike pain developed in the epigastrium and the left upper quadrant of the abdomen, aggravated by deep breathing and associated with nausea and vomiting. The symptoms increased in severity until the time of admission. There was no bowel movement or passage of flatus during this attack.

*Physical Examination.*—The patient was a moderately obese, acutely ill white woman of stated age in mild distress. The temperature was 37.6 C. (99.7 F.), and the blood pressure was 125 systolic and 85 diastolic. The skin and the mucous membranes showed moderate dehydration. The abdomen was slightly distended and tense with diffuse tenderness in the left upper quadrant, muscle spasm and rebound tenderness. A questionably cystic mass, extending from the left flank to the midline and from the costal margin to the umbilicus could be outlined only with difficulty because of tenderness. No bruit or fluid was present. There was an umbilical hernia with a defect of 2 by 2 cm. Pelvic and rectal examinations were negative.

*Laboratory Findings.*—The urine gave a 3 plus reaction for sugar and a 2 plus reaction for acetone. The blood findings were: hemoglobin content, 14 Gm.; red blood cell count, 4,900,000; white blood cell count, 13,000. The Kline test was negative; the blood urea nitrogen was 13 and the blood sugar 237 mg. per hundred cubic centimeters.

*Röntgen Examination.*—A flat plate of the abdomen showed a soft tissue mass in the left upper quadrant not associated with the kidney or the spleen. A chest plate was negative except for pleural thickening. A gastrointestinal series showed the stomach to be displaced cephalad and anteriorly, but no intrinsic lesion was demonstrable. An enema of barium sulfate revealed the splenic flexure and the transverse colon to be displaced caudad. Intravenous pyelograms revealed that

the left renal pelvis never visualized satisfactorily. What could be seen of the upper calices did not appear abnormal. The kidney was of usual length and width. These findings led us to believe that the condition arose from the retroperitoneal space, with the left kidney and the tail of the pancreas recognized as the most likely sites of origin. Because of the downward displacement of the splenic flexure and the transverse colon and the medial and upward displacement of the stomach, the body or the tail of the pancreas seemed to be the probable site. The fact that the tumor was of a cystic nature suggested that we were dealing with a cyst in the body or the tail of the pancreas.

*Hospital Course.*—The patient was kept in bed and the diabetes regulated while the studies just mentioned were carried out. The pain, nausea and vomiting subsided, and the mass in the upper part of the abdomen became more readily outlined as the tenderness subsided.

*Operation.*—On the seventh day after admission, with the patient under anesthesia induced with open drop ether, an upper left rectus incision was made, and a large mass was encountered. It appeared to be beneath the gastrocolic omentum, which was stretched to allow for the displacement of the stomach and the transverse colon, and the significant finding was the tremendous enlargement and obvious dilatation of the blood vessels. After separating the gastrocolic omentum, the mass could be readily seen. It was roughly round, had a poorly circumscribed outline, was cystic to palpation and was only slightly movable. A large vein, 1 cm. in diameter, coursed transversely and obliquely over the anterior surface of the cyst. An incision was made into the cyst and about 1 liter of thick, glairy, curdlike fluid was aspirated. This collapsed the mass sufficiently to allow better inspection of the surroundings. The large vein was thought to be the splenic and was clamped, divided and ligated when it became obvious, after an attempt to dissect it off the mass, that it had to be sacrificed in order to remove the tumor successfully. By sharp and blunt dissection and further freeing of the vessels, the third portion of the duodenum was separated from the mass. It now became apparent that the growth arose from the pancreas in a broad pedicle involving the outer third and the tail of the organ. It was necessary to remove a small amount of the pancreas with the cyst, and this was accomplished without injury to the large pancreatic duct. Transfixion sutures were placed in the cut areas of the pancreas. Careful inspection was made to determine whether any other major vessels had been injured, and it was possible to show that the middle colic artery, the splenic artery and the portal vein had been preserved. We were correct in our assumption that the large vein which had been ligated was the splenic vein. As the spleen was enlarged to three times its normal size, splenectomy was performed. Four cigaret drains were inserted, and the abdomen was closed with through and through sutures of silver wire. The patient was in moderate shock during the latter third of the operation and on the operating table received a transfusion of 1,000 cc. of blood.

*Postoperative Course.*—Since the patient was in moderate shock, she was given oxygen by mask and 500 cc. of blood. The next day her condition was good. The diabetes, which was easily controlled for the first forty-eight hours, became difficult to manage for the next forty-eight hours. From the fifth day on, the patient's condition progressively improved so that 10 units of protamine zinc insulin sufficed to control the diabetes at the time of discharge instead of the 35 units of unmodified insulin and 10 units of protamine zinc insulin which previously had been required.

The serum amylase was 13 units per cubic centimeter on the third postoperative day; two weeks later, it was 100 units, and five days before discharge, it was 40 units.

The wound drained moderate amounts of serosanguineous fluid. Two drains were removed on the tenth, and the remaining two, on the eighteenth postoperative day. The silver wire sutures were removed on the twentieth postoperative day. At the time of discharge, the wound was healed except for a sinus tract, 4 cm. in depth and 0.6 cm. in diameter. There was never any excoriation of the skin.

*Pathologic Findings.*—Gross: The cyst measured 15 by 10 by 10 cm. The lining was smooth but with heavy pillow-like masses which contained fluid and represented daughter cysts. The outside of the cyst was smooth and well encapsulated. The spleen weighed 419 Gm. and measured 19 by 10 by 4.5 cm. The parenchyma was dark red with prominent follicles.

*Microscopic:* The cysts were lined with columnar epithelium thrown into irregular folds. The cells were regular, well differentiated and high columnar. The spleen showed questionable miliary tubercles.

*Follow-up Examination.*—Six weeks after discharge her condition was excellent. The diabetes was controlled by 10 units of protamine zinc insulin a day. The sinus tract had practically healed.

CASE 2.—A. M., a white Danish-born woman 44 years of age, was admitted to the New York Hospital on Sept. 29, 1932, with a history of fatigue associated with vague abdominal distress and constipation of two years' duration. The past history was negative except that she had had adequate treatment for syphilis during the past three years.

The physical examination was essentially negative except for the abdomen, in which a well defined mass was felt in the left upper quadrant, extending from the costal margin to the midline. The mass was nontender and freely movable and descended slightly with inspiration.

The laboratory examinations were essentially negative except for the blood sugar, which ranged from 241 to 111 mg. per hundred cubic centimeters with decreased dextrose tolerance. A roentgen gastrointestinal series showed the stomach displaced to the left and downward by a mass superior to the lesser curvature. An enema of barium sulfate revealed the transverse colon to be displaced caudad.

*Operation.*—At operation through a left paramedian incision, a large (12 by 8 by 5 cm.) cyst arising from the midportion of the pancreas was removed through the gastrohepatic omentum. The wound was closed without drainage.

*Pathologic Findings.*—Gross: The specimen consisted of a cystic mass, 12 by 8 by 5 cm., with a small amount of pancreatic tissue attached to the posterior surface. The cyst was multilocular and was composed of two parts—a larger coalesced mass of cysts which was thin walled and blue and contained yellowish fluid and a rounded mass of small thin-walled cysts from a few millimeters to 3 cm. in diameter. It was transparent and white and contained a colorless fluid.

*Microscopic:* Microscopic examination showed a multilocular cyst lined with low cuboid epithelium thrown into papillary projections.

*Postoperative Course.*—During the postoperative course there was transient slight glycosuria and moderate acidosis. The wound healed by first intention.

*Follow-up Examination.*—Follow-up examination revealed that the patient had slight discomfort in the left upper quadrant of the abdomen for the first few months after operation. She had been in excellent health for the past eight years at the time of her last visit in July 1941.

CASE 3.—N. C., a white Russian-born Jewish woman 42 years of age, was admitted to the New York Hospital on May 18, 1934, with a history of attacks of epigastric pain radiating to the back and occurring approximately every month and lasting one to two days over the preceding four and a half years. During the seven months before admission, she had dull epigastric pain associated with frequent loose, foul stools. The latter cleared up after a few months. For several weeks before admission, the patient had noted a mass in the epigastrium.

The physical examination revealed an emaciated, chronically ill woman. The thorax was rachitic in contour. In the abdomen there was a visible epigastric mass which, on palpation, was nodular, measured 10 by 6 cm., was firm, nontender and immovable and transmitted the aortic pulsation.

The laboratory examinations were essentially negative except for the finding of decreased dextrose tolerance. A roentgen chest plate revealed soft mottling of the apexes, representing questionable tuberculosis. A gastrointestinal series showed the stomach to be displaced to the left by a mass, and a roentgenogram taken twenty-four hours after the gastrointestinal series showed the transverse colon to be depressed caudad.

*Operation.*—At operation, through a left rectus incision, a lobulated mass, 18 by 12 by 15 cm., was found lying in the region of the pancreas. The gallbladder was normal except for adhesions around it. A large (1 to 1.5 cm.) vein traversing the cyst was torn. By the time the hemorrhage was controlled, the patient had lost so much blood that she was in shock, and the procedure had to be abandoned. The abdomen was closed without drainage.

*Postoperative Course.*—During the postoperative course the patient failed to respond to multiple transfusions. Oliguria, renal and cardiac failure developed, and she died forty-eight hours after the operation. Permission for postmortem examination was refused.

CASE 4.—A. C., a white Irish-born woman 66 years of age, was admitted to the New York Hospital on Sept. 6, 1938, with a history of pain in the right upper quadrant of the abdomen associated with nausea and eructation and aggravated by the ingestion of fatty and greasy foods. All symptoms were worse during the seven months before admission. The gallbladder showed a fairly good roentgen shadow. For twenty years, she was known to have duodenal ulcer; this was interpreted as healed on roentgen examination shortly before admission. One and a half years before admission, a carcinoma of the cervix was treated with radium. There were no further clinical manifestations relative to this lesion.

The physical examination showed a thin well preserved woman. The heart sounds were of poor quality. The abdomen was soft with moderate tenderness in the right upper quadrant, and the edge of the liver was felt 3 cm. below the right costal margin. No mass was felt. Pelvic examination showed a firm band of scar tissue in the vagina, but the cervix was not seen or felt.

The preoperative laboratory examinations were essentially negative. A roentgenogram of the chest was negative, and a cholecystogram showed a normal gallbladder. A gastrointestinal series revealed a defect in the duodenal cap, but no soft tissue mass was seen. An enema of barium sulfate was not given.

*Operation.*—At operation the abdomen was opened through a right rectus incision. The liver showed a slight degree of cirrhosis, and the gallbladder was large. A tumor, 8 by 7 by 5 cm., lay beneath the stomach. This was attached to the body of the pancreas and was removed through a rent in the gastrocolic omentum. A large vein (the splenic) was incorporated in the wall of the cyst posteriorly. The



cyst was removed without injuring the vein. The gallbladder was removed, and one drain was inserted down to the foramen of Winslow.

*Pathologic Findings.*—Gross: The specimen was a thin-walled, lobulated cyst containing saliva-like fluid with milky sediment. Several calculi, approximately 1 mm. in diameter, were present in the wall.

*Microscopic:* The cyst was lined by high cuboid epithelium.

*Postoperative Course.*—During the postoperative course, the patient developed high blood and urine amylase with evidence of fat necrosis in the drainage. On the eleventh postoperative day there was noted in the left upper quadrant of the abdomen an abscess which necessitated drainage five days later. It was thought that the abscess was due to pancreatic damage and fat necrosis. The course was satisfactory after drainage, and the sinus tract healed completely two weeks after discharge from the hospital.

*Follow-up Data.*—The patient was known to be in excellent health at the time of her last report by letter, two years after operation.

CASE 5.—J. J., a white Gibraltar-born woman 54 years of age, was admitted to the New York Hospital on Jan. 4, 1939, with a history of a mass in the left upper quadrant of the abdomen of four years' duration, increasing in size slowly for three and one-half years and rapidly for the five months prior to admission. The patient had a dragging sensation in the back and had lost 20 pounds (9.1 Kg.). She had a "binding feeling" on defecation. The only relevant finding in the past history was that she had had an appendectomy fourteen years before admission.

The physical examination revealed a thin elderly appearing woman. The fundi showed arteriosclerotic changes of moderate degree. The abdomen was asymmetric, and there was a firm, slightly tender, movable mass, 19 by 15 cm., extending from the left costal margin to the midline and to the left flank. There was no bruit or expansile pulsation. There was a right rectus scar with a fascial defect, 8 by 5 cm. in diameter.

Laboratory examinations were entirely negative except for the stools, which gave a 2 plus reaction for benzidine. A chest plate roentgenogram was negative. A roentgen gastrointestinal series showed the stomach to be displaced medially and anteriorly. An enema of barium sulfate showed the transverse and descending parts of the colon displaced laterally and downward. Intravenous pyelograms were negative except for a soft tissue mass in the left upper quadrant of the abdomen below the spleen.

*Operation.*—At operation through a left rectus incision, a cystic mass arising from the tail of the pancreas was removed through a rent in the gastrocolic omentum. The abdomen was closed without drainage.

*Pathologic Findings.*—Gross: The cyst measured 18 by 12 by 13 cm. and weighed 1,805 Gm. It was multilocular with cysts averaging 3 cm. in diameter and filled with thick mucoid material, some of which appeared puriform.

*Microscopic:* The cyst was lined by high columnar epithelium which resembled gallbladder mucosa.

*Postoperative Course.*—The postoperative course was uneventful. The wound healed by first intention.

There was an attack of catarrhal jaundice with prompt recovery three months after operation.

*Follow-up Examination.*—She was in excellent health on July 1, 1941, two and one-half years after operation.

## COMMENT

Certain significant findings which these cases have in common are shown in table 1, reference to which reveals that a definite history of antecedent biliary tract disease was present in 4 of the 5 cases. The rela-

TABLE 1.—*Diagnostic Features in Cystadenoma of the Pancreas*

Case	History of Biliary Tract Disease	Mass	Diabetes	Roentgen Examination of Diagnostic Value	Splenic Vein at Operation
1	Typical	Present	Moderate	Yes	Traversing cyst anteriorly
2	Suggestive	Present	Mild	Yes	No statement
3	Typical	Present	Mild	Yes	Traversing cyst anteriorly
4	Typical	No mass	None	No	Traversing cyst posteriorly
5	None	Present	None	Yes	No statement

TABLE 2.—*Data Obtained by Roentgen Examinations*

Case	Soft Tissue Mass	Gastrointestinal Series	After Enema of Barium Sulfate	Pyelogram
1	Seen in the left upper quadrant of the abdomen; not associated with the kidney or the spleen	Stomach displaced cephalad and anteriorly	Splenic flexure and transverse colon displaced caudad	Preoperative: left side never filled Postoperative: left side filled normally Right side normal throughout; (urologic opinion: pressure on blood supply)
2	Superior to the lesser curvature in the left upper quadrant of the abdomen	Stomach displaced to the left, downward, and elongated	Transverse colon depressed caudad	None
3	Superior to the lesser curvature in the left upper quadrant of the abdomen	Stomach displaced to the left and elongated	Transverse colon depressed caudad	None
4	None seen	Stomach not displaced	None	None
5	Seen in the left upper quadrant of the abdomen below the spleen	Stomach displaced medially and anteriorly	Transverse and descending colon depressed laterally and caudad	Normal

tion of disorders of the biliary tract to cystadenoma of the pancreas is of diagnostic interest, but from the viewpoint of pathogenesis its significance is open to question.

The only other finding of note in the history was the presence of an abdominal mass which had been observed for four years in 2 cases and

seven weeks in 1 case. No mass was noted by the patients in the other 2 cases.

All 5 of the patients were women whose ages ranged from 37 to 66 years.

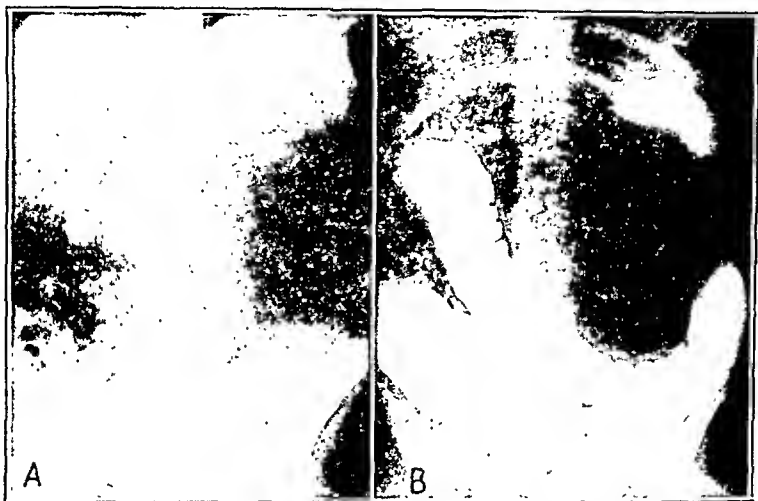


Fig. 1 (case 5).—Roentgenograms: *A*, from the gastrointestinal series showing displacement of the stomach medially by the pancreatic cyst; *B*, after an enema of barium sulfate showing displacement of the colon downward by the pancreatic cyst.

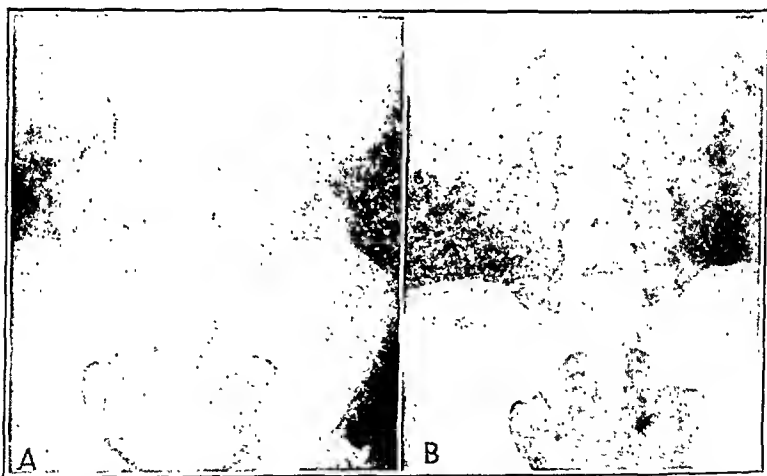


Fig. 2.—Intravenous pyelograms: *A*, preoperative, showing poor filling of the left renal pelvis (case 1); *B*, postoperative, showing normal filling of each renal pelvis (case 2).

The most important physical finding was the presence of a palpable, sometimes visible, mass in 4 of the 5 cases. The mass varied in size from 19 by 15 to 10 by 6 cm. In 2 of the 4 cases, the mass was movable; in

the other 2 it was fixed. In case 1, the mass was extremely tender on admission, but this was due to leakage of the cyst as was demonstrated at operation. The tenderness subsided during the preoperative course. Of the 3 remaining cases in which a mass was palpable, slight tenderness was present in only 1.

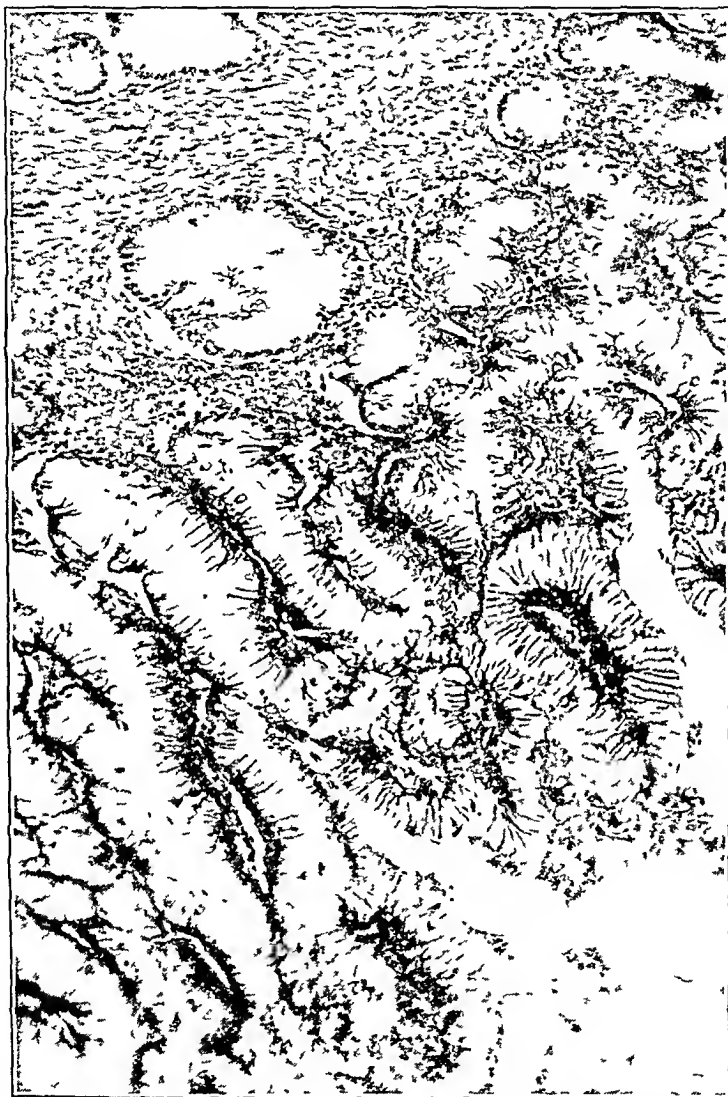


Fig. 3 (case 1).—High power photomicrograph showing tall columnar epithelium lining the folds of a cystadenoma

Laboratory examination showed moderate diabetes in 1 case, mild diabetes in 2 cases and normal urine and blood sugar in 2 cases. In 2 cases there was increased severity of the diabetes shortly after operation. However, these manifestations were readily controlled. In 1 of the cases

(case 1), the diabetes was less severe at the time of discharge than it had been during the preoperative phase.

The most valuable laboratory test was the roentgen examination. As can be seen in table 1, roentgen examination was of diagnostic value in 4 of the 5 cases. In table 2, the results of the various roentgen examina-



Fig. 4 (case 2).—High power photomicrograph showing low cuboid epithelium lining the cyst wall.

tions are shown. A soft tissue mass could be seen in the left upper quadrant of the abdomen in 4 of the 5 cases. In case 1, this shadow was distinguishable from those of the kidney and the spleen. Gastrointestinal series were made in all cases; in 4 there was definite displacement of the

stomach (fig. 1 *A*). The direction of the displacement varied from one case to another. Enemas of barium sulfate were given in 4 of the 5 cases; in all 4 the transverse colon was displaced caudad (fig. 1 *B*). Intravenous pyelograms were made of 2 patients; in 1, the shadows were normal, and in the other there was poor function of the left kidney and



Fig. 5 (case 4).—Low power photomicrograph showing high cuboid epithelium lining the cyst. On the other side of the photomicrograph pancreatic acini are shown.

incomplete filling of the pelvis without change in its size or position. It was the clinical impression that pressure by the cyst on the renal artery or vein or both was the cause of this finding. This impression was proved subsequently by postoperative pyelograms which showed normal function of the left kidney and no filling defect (fig. 2).

An operative finding of great significance in this series of cases was the presence of a dilated splenic vein intimately associated with the wall of the cystadenoma of the pancreas in 3 of the 5 cases. Our attention was called to this finding most vividly by the most recent case in the group (case 1). In this instance, the splenic vein was adherent to the anterior wall of the cyst, crossing it transversely. During the course of the removal of the cyst, the splenic vein was injured and bled profusely until controlled by clamping. Following extirpation of the cyst, the spleen was found to be enormously enlarged; it was then removed. In retrospect, it is seen that removal of the cyst might have been facilitated by first removing the spleen. The great practical importance of this fact is seen in case 3, in which injury to this vein resulted in the death of the patient from hemorrhage and shock. In 1 other case, the vein was seen crossing the cyst anteriorly; in another it was found posterior to the cyst.

The gross and the microscopic pathologic appearance of these specimens were constant. The cysts were smooth, well encapsulated, multilocular and filled with clear or turbid fluid. Two of the cysts arose from the body and 2 from the tail of the pancreas far enough for the origin to be determined. The photomicrographs show the typical microscopic findings of true cystadenoma of the pancreas (figs. 3, 4 and 5). The cyst lining was of high columnar or cuboid epithelium with clear cytoplasm and basal nuclei. The lining was thrown into papillary projections. All 4 of the specimens showed this picture. Although no pathologic specimen was obtained in case 3, it is included in the series of cases because the clinical, roentgen and operative findings strongly suggested the diagnosis of cystadenoma.

#### SUMMARY

Five cases of cystadenoma of the pancreas are presented.

The significance of the history of antecedent disease of the biliary tract and of the presence of a mass in the upper part of the abdomen is emphasized.

Diabetes was present in 3 of the 5 cases, with improvement in the late postoperative period in 1.

Roentgen studies, such as gastrointestinal series, roentgenograms taken after enemas of barium sulfate and intravenous pyelograms, are of importance in establishing the diagnosis.

The intimate relation of the splenic vein to the wall of the cyst and the importance of its recognition during extirpation of the cyst are discussed.

# FAMILIAL POLYPOSIS OF THE COLON

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URBANA, ILL.

By definition, polyposis of the colon is a condition in which adenomatous tumor grows from the wall of the bowel and projects into the lumen. Most authors adhere to the classification of Erdmann and Morris,<sup>1</sup> which divides polyposis into two types: (1) the adult or acquired type, which usually follows a chronic inflammatory process, such as chronic ulcerative colitis, tuberculosis or amebiasis; (2) the familial type, which involves the entire colon and rectum of young adults and shows a definite hereditary tendency. It is with this second type that this study is concerned.

The condition of polyposis was first described by Virchow<sup>2</sup> in 1863, and Cripps<sup>3</sup> presented 2 cases in 1882 in which he noted the hereditary factor. Since that time many studies have been published in the literature, and the heredofamilial malignant aspect of some cases has been emphasized. McKenney<sup>4</sup> studied three family groups, a total of 52 persons, and found 21 patients (40.39 per cent) with multiple polyposis; 8 of these (38.09 per cent) died of carcinoma of the rectum or the colon. In 1 of his patients malignant growth was found at the age of 15 years. The youngest patient was 2 years old, and 3 older children in the same family showed progressive increase in the size of the polyps. Lockhart-Mummery,<sup>5</sup> who also has presented studies of three families, expressed the belief that the condition is inherited as a mendelian dominant characteristic but that children are not born with it. Mayo and Wakefield,<sup>6</sup> Coffey and Barger,<sup>7</sup> Hullsieck,<sup>8</sup> Rankin and Grimes,<sup>9</sup> Miller and Sweet<sup>10</sup> and Janssen<sup>11</sup> have all presented similar cases.

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From the Department of Surgery, Carle Memorial Hospital.

1. Erdmann, J. F., and Morris, J. H.: Polyps of the Colon, Surg., Gynec. & Obst. **40**:460-468 (April) 1925.

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(Footnotes continued on next page)



The purpose of this article is to study a family of 7 children in which 6 showed multiple polyps of the colon; 2 of these children died after carcinomatous degeneration.

#### FAMILIAL HISTORY

The paternal grandfather died at the age of 30 of cholera morbus. The significance of this can only be speculated on, but it is of interest in a family with a history such as this. The two doctors who attended him have long since died, and the only information available is that he died after an illness of fourteen hours' duration, having been previously in excellent health. The paternal grandmother died at the age of 32 of pulmonary tuberculosis. There were 4 sons in this family; 1 died at 30

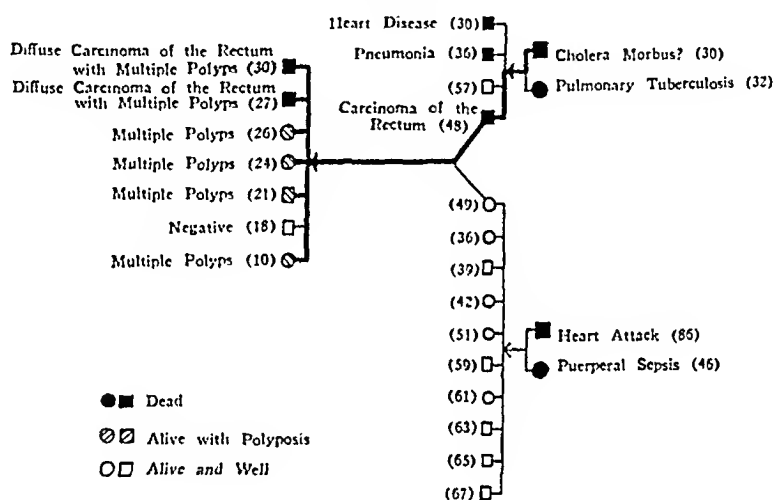


Chart showing familial history of polyposis of the colon. Squares indicate male, and circles female, members of the family; the ages are given in parentheses.

of heart disease; 1, at 36 of pneumonia; 1 is living and well at the age of 57 at the time of writing, and the fourth was the father of the 7 children in this study. The last named was seen elsewhere at the age of 47 with advanced carcinoma of the rectosigmoid. His wife relates that

7. Coffey, R. J., and Bagen, J. A.: Intestinal Polyps: Pathogenesis and Relation to Malignancy, *Surg., Gynec. & Obst.* **69**:136-145 (Aug.) 1939.

8. Hullsiek, H. E.: Multiple Polyposis of the Colon, *Surg., Gynec. & Obst.* **47**:346-356 (Sept.) 1928.

9. Rankin, F. W., and Grimes, A. E.: Diffuse Adenomatosis of the Colon, *J. A. M. A.* **108**:711-715 (Feb. 27) 1937.

10. Miller, R. H., and Sweet, R. H.: Multiple Polyposis of the Colon: Familial Disease, *Ann. Surg.* **105**:511-515 (April) 1937.

11. Janssen, C. L.: Familial Polyposis of the Colon with Carcinoma of the Rectum and Sigmoid, *Ann. Surg.* **95**:279-282 (Feb.) 1932.

he had had a twenty-four year history of diarrhea with blood and mucus in the stools and was known also to have "hemorrhoids" for many years. Although a diagnosis of multiple polyposis cannot be established, the history is typical of the condition. He died at the age of 48.

The maternal side presents an essentially negative history. The grandfather died at 86 after a heart attack and the grandmother at 46 of puerperal sepsis. There were 12 children on this side of the family; 2 died in infancy, and the rest are all living and well at the time of writing. The mother has always been well, and examinations of the colon and sigmoidoscopic examinations were negative.

#### REPORT OF CASES

CASE 1.—L. O'D., a 28 year old white man, was the first of the family to come to my attention. He was brought by ambulance to the Carle Memorial Hospital on Oct. 7, 1940, in a nearly comatose condition. The following history was obtained from the family: The patient, formerly a machinist, had been well until early in 1938 (two and one-half years previous to admission), when he complained of weakness and frequent loose stools accompanied by cramping pain. Blood had been noted in the stools several times. His local physician examined him and found "hemorrhoids and a small rectal tumor," which the physician fulgurated. He continued to have three or four loose stools a day, but the attacks of cramping pain were less frequent until about six months before admission, when he complained of bloating. Diarrhea and tenesmus then became worse. He had a roentgen examination of the colon which showed generalized polyposis. His physician advised surgical intervention and performed ileosigmoidostomy. The walls of the colon were found to be thick and uniformly studded with small round pea-sized polyps projecting from the mucosa into the lumen. Ileosigmoidostomy was followed by partial colectomy in two later stages. The patient fared badly after this series of operations, and when first seen at the Carle Memorial Hospital, he appeared markedly emaciated, cyanotic and dehydrated, and vascular collapse seemed imminent. There were multiple small bowel fistulas draining through the wall of the abdomen, and he had many loose stools daily in addition to copious drainage from the fistulas. Proctoscopic examination revealed a firm, somewhat fixed stenosing lesion in the rectum. Biopsy of this mass showed grade 2 adenocarcinoma. Peritonitis developed, and the patient died.

CASE 2.—L. L. O'D., a 30 year old brother of the patient in case 1, came to the clinic for examination on March 16, 1941 at my request. He had been well until 1938, when he had a brief episode of nausea, vomiting and diarrhea with cramping and bloody stools. In July 1939, he again had fever, nausea, vomiting and severe pain in the lower part of the abdomen. His physician noted marked abdominal distention and rigidity. Abdominal exploration was done to determine the cause of the peritonitis. A right rectus incision was made, and perforating carcinoma of the descending colon was found. Then through a left rectus incision the first stage of the Mikulicz operation was performed. On the following day, the tumor was removed by electrocautery. Later, cecostomy was done, and anastomosis was established between the proximal portions of the transverse colon and the rectum. Finally, the distal portion of the transverse colon and the descending colon were removed. After this, the patient got along well and returned to work. Later roentgen studies showed polyps in the remaining parts of the colon and

the rectum. The rectal polyps were cauterized and the "internal hemorrhoids injected." By the middle of 1940 he was complaining of pain low in the back and severe constipation. At the time of examination at the clinic, he was having seven or eight loose stools a day and was experiencing difficulty in starting the urinary stream. The wall of the abdomen showed multiple scars. On rectal examination there was a hard, baseball-sized mass in the prostatic region, blocking the rectum. Proctoscopic examination could not be attempted, but roentgen studies with barium sulfate contrast medium revealed extensive ulcerated carcinoma of the rectosigmoid. He was undergoing a series of roentgen treatments elsewhere at that time, but he has since died.

CASE 3.—M. O'D. H., a 26 year old sister of the patients in the first 2 cases, also came to the clinic for study at my request. Shortly after parturition in 1936, she began to have one to three watery stools a day. There was never any blood, but frequently mucus was noted. Three years later, she complained of generalized weakness and easy fatigability. Study of the colon in 1940 revealed generalized polyposis. Her physician did a first stage ileosigmoidostomy in August 1940, and she convalesced rapidly. At the time of writing she is having three to five soft stools a day. Her weight now is 99 pounds (45 Kg.). An enema of barium sulfate was given, and the ileocolostomy was found to be functioning well with innumerable polyps scattered throughout the colon. She stated that she "will never be operated on again." She was married and had one child.

CASE 4.—E. O'D. H., a 24 year old sister of the patients in the other 3 cases, came to the hospital on Jan. 21, 1941. She had no children. Because of diarrhea, the colon had been studied elsewhere, and a diagnosis of diffuse polyposis of the colon had been made. Proctoscopic examination here showed multiple polyps as large as 1.5 cm. in diameter. She was advised to undergo total colectomy, and on March 11 permanent ileostomy was established through a McBurney incision. Recovery was uneventful, and at the time of writing, the patient feels much better. It is expected that she will submit to the remaining stages of operation (total colectomy and posterior resection) in the near future.

CASE 5.—D. O'D., a 21 year old mechanic, was a brother of the previous 4 patients. He had no children. He submitted to examination at my request. He had always been well and presented no complaints. His history was generally noncontributory, and there were no bowel symptoms. Physical examination was likewise negative save for the rectum, in which many polyps were palpable, beginning about an inch (2.5 cm.) above the dentate margin. Sigmoidoscopy showed many polyps. The largest were about 8 mm. in diameter; many were pedunculated, and some occurred in clusters. Roentgen examination of the colon showed multiple polyps scattered through the large bowel except in the cecum and the ascending portion of the colon. At the time of writing, he is undecided about submitting to operation.

CASE 6.—V. O'D., a 10 year old schoolgirl and a sister of the other 5 patients, came to the clinic on March 16, 1941 for examination with the remainder of the family. The colon had been studied elsewhere and was believed to be normal. Two years previously, she had had an episode of cramping in the lower part of the abdomen associated with diarrhea, which persisted for about six weeks. She has no complaints at the time of writing and is gaining weight steadily. The colon was restudied here, and the roentgenologist stated that there were questionable minute polyps in the descending and the sigmoid colon. However, on sigmoidoscopy many tiny polyps were visualized which were about 3 mm. in

diameter. The family has been advised to have the roentgen and sigmoidoscopic examinations repeated annually and to consider operation after the child has passed adolescence.

CASE 7.—L. E. O'D. was 18 years old and a brother of the other 6 patients. His entire history and physical examination were negative. Roentgen examination of the colon and sigmoidoscopy were negative. Of the 7 children, this boy appeared to be the sturdiest. He was married and had one child.

#### DIAGNOSIS

The symptoms and signs commonly found include diarrhea, intermittent blood in the stools, abdominal cramping, loss of weight and anemia. Polyps may be palpable in the rectum, but sigmoidoscopy and roentgen examination of the colon establish the diagnosis definitely and reveal the extent of the disease.

#### TREATMENT

From a study of the literature it appears that carcinomatous degeneration of the polypi occurs frequently in cases of this disease. It is for this reason that total colectomy is considered the only satisfactory treatment. The most common procedure is that of establishing permanent ileostomy to divert the fecal stream, and after a satisfactory convalescence this is followed by total colectomy and finally by posterior resection of the rectum. Mayo and Wakefield<sup>12</sup> presented another method of treatment for use in selected cases. The rectum, the rectosigmoid and the sigmoid are first cleared of polyps by the repeated use of diathermy, only a few polyps being removed at a time. The second stage consists of end to side ileosigmoidostomy and hemicolectomy. As soon afterwards as possible, the third stage is carried out. This again consists of hemicolectomy with removal of the remaining transverse colon, the splenic flexure and the descending colon. Smith<sup>13</sup> observed a patient treated in this way for eight years; the patient returned frequently for fulguration of any new polyps but was able to return to heavy work.

McKenney<sup>14</sup> treated a number of patients with radiation therapy and reported that the number and the size of the polyps decreased but withheld recommendation of roentgen therapy until the results have been further evaluated.

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12. Mayo, C. W., and Wakefield, E. G.: Disseminated Polyposis of the Colon: A New Surgical Treatment in Selected Cases, *J. A. M. A.* **107**:342-348 (Aug. 1) 1936.

13. Smith, N. D.: Polypoid Disease of the Colon and Terminal Ileum: Observation of a Case for Eight Years, *Proc. Staff Meet., Mayo Clin.* **14**:255-256 (April 9) 1939.

14. McKenney, D. C.: Multiple Polyposis of the Colon: Familial Factor and Malignant Tendency, *J. A. M. A.* **107**:1871-1876 (Dec. 5) 1936.

## SUMMARY

In a family of 7 children 6 were found to have polyposis—an incidence of 85.7 per cent. Among the 6 patients, there were 3 males and 3 females. In 2 (33 per cent), malignant change developed in the polyps. Both malignant changes were in males, but these were the oldest children.

The average age of the 6 is 19.7 years; the oldest was 30 and the youngest 10. None exhibited symptoms before the age of 23. The polyps in the younger children were proportionally smaller.

The father of these children died at the age of 48 of carcinoma of the rectum after a twenty-five year history suggestive of multiple polyposis. The paternal grandfather died at 30 of "cholera morbus"—an interesting fact.

Operation in 2 of these cases gave unsuccessful results. In both cases carcinomatous changes took place in the rectum. In a third case permanent ileostomy was done, and the patient will probably submit to total colectomy and posterior resection.

The 10 year old patient will be followed closely, and operation will be considered after she has matured.

Several of these patients have young children; these will present an interesting subject of study after a few years.

## CONCLUSIONS

The type of polyposis presented in these cases is a hereditary condition.

Malignant degeneration of the polyps is frequent in cases of polyposis of the colon.

Early and radical operation is the treatment of choice.

# GANGLION CELL TUMOR (GANGLIOGLIOMA) IN THE THIRD VENTRICLE

OPERATIVE REMOVAL WITH CLINICAL RECOVERY

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AND

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LOS ANGELES

Ganglion cell tumors of the brain are not common. However, owing to increasing interest in the subject during the past ten years these growths are now known to be less rare than once was believed. In 1937, Wolf and Morton<sup>1</sup> reviewed 48 cases of intracranial ganglion cell neoplasm found in the literature and added 2 of their own. In 14 cases in their review, the tumor arose in or near the third ventricle; the first case of this kind was described by Robertson in 1915.

No successful removal of a ganglion cell tumor in the third ventricle has been reported. The patient of Alpers and Grant<sup>2</sup> failed to survive partial extirpation. Dandy,<sup>3</sup> in his monograph, reported no cases of this kind, although in 3 of the cases he reported there were solid growths of uncertain cellular type resembling pineal tissue. In the majority of cases in which tumor in the third ventricle has been successfully operated on, the growth has been a so-called colloid cyst.

## LITERATURE

The subject of ganglion cell tumor of the central nervous system was reviewed at length by Courville<sup>4</sup> in 1930 with the presentation of

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1. Wolf, A., and Morton, B. F.: Ganglion Cell Tumors of the Central Nervous System, *Bull. Neurol. Inst. New York* 6:453, 1937.

2. Alpers, B. J., and Grant, F. C.: The Ganglioneuromas of the Central Nervous System, *Arch. Neurol. & Psychiat.* 26:501 (Sept.) 1931.

3. Dandy, W. E.: Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

4. Courville, C. B.: Ganglioglioma, Tumor of the Central Nervous System: Review of the Literature and Report of Two Cases, *Arch. Neurol. & Psychiat.* 24:439-491 (Sept.) 1930; Gangliogliomas: A Further Report with Special Reference to Those Occurring in the Temporal Lobe, *ibid.* 25:309 (Feb.) 1931.

2 cases and a summary of the 18 cases reported up to that time. He recommended the name "ganglioglioma," as first suggested by Ewing, because it indicates the two essential constituents of this neoplasm, i. e., ganglion and glial cells. Alpers and Grant also reviewed the literature on the subject and presented a case in which such a tumor arose from the floor of the third ventricle; the patient failed to survive exploratory operation. They expressed preference for the term "ganglioneuroma," as proposed by Pick and Bielschowsky<sup>5</sup> in 1911, because of the inherent simplicity of such a classification.

Seven cases of intracranial ganglion cell tumor were presented by Kernohan, Learmonth and Doyle.<sup>6</sup> In 2 of these cases, the tumor originated in the floor of the third ventricle. These authors used the terms "neuroblastoma" and "gangliocytoma," depending on the maturity of the ganglion cells.

An excellent review with a detailed consideration of the histopathology and a presentation of 2 cases is that of Wolf and Morton.<sup>1</sup> They offered a classification based on predominant cell types and cited two major groups: (1) the comparatively pure ganglion cell tumors—ganglioneuroblastoma and gangliocytoma, depending on cell maturity—and (2) the mixed ganglion cell and glial tumor, which include ganglioglioblastoma and ganglioglioma.

The commonest site of origin of these tumors in the brain is the region which, for purposes of classification, has been designated as the floor of the third ventricle. The next most common location is apparently the temporal lobe. This type of tumor occurs most frequently in young persons; a few cases have been reported in which the patients were over 40 years of age, but the majority are younger than that, and in about 60 per cent of the reported cases the patients are under 30 years of age.

Judging from the clinical and the pathologic picture, the tumor can be considered relatively benign. The duration of symptoms varies greatly but is recorded as high as sixteen years, and a span of two or three years is not uncommon. In a few cases, however, symptoms were noted only a few weeks before death. Wolf and Morton found a definite correlation between the microscopic appearance of the specimen and the clinical course, the duration of symptoms averaging eleven months for the more malignant ganglioneuroblastoma and five and one-tenth years for the mature variety, the ganglioglioma. Of course, the location of the lesion

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5. Pick, L., and Bielschowsky, M.: Ueber das System der Neurome und Beobachtung an einem Ganglioneurom des Gehirns nebst Untersuchung über die Genese der Nervenfasern in "Neurinomen," *Ztschr. f. d. ges. Neurol. u. Psychiat.* 6:391, 1911.

6. Kernohan, J. W.; Learmonth, J. R., and Doyle, J. B.: Neuroblastomas and Gangliocytomas of the Central Nervous System, *Brain* 55:287, 1932.

creates a variable in any such estimation. In our patient, although the tumor arose within the third ventricle, symptoms had been present for at least three years.

In most instances, the neoplasm has been found at operation or necropsy to be fairly sharply demarcated from the brain substance and to have little tendency toward invasion. However, at times the mass is irregular with no boundaries and a strong tendency to invade the adjacent portion of the brain, as in 4 of the 6 cases presented by Kernohan, Learmonth and Doyle.<sup>6</sup> The microscopic picture in general has not given the appearance of a rapid growth but rather has tended to classify the mature varieties as fairly benign.

#### PATHOLOGIC DESCRIPTION

The pathologic characteristics have been discussed in detail by Courville, Wolf and Morton, Kernohan and others. Grossly, the tumor is usually gray, although sometimes it is multicolored, with areas of yellow pigmentation and hemorrhage. As mentioned previously, the mass is frequently, but not always, encapsulated; cyst formation is common, as are central necrosis and softening.

On microscopic examination, the striking feature is the presence of ganglion cells. These vary in size, shape and maturity, have one or more pale-staining nuclei and usually contain Nissl substance. Lymphocyte-like cells are usually found; the precise identity of these is not clear. They tend to be perivascular or diffuse and have been called "neuroblasts,"<sup>6</sup> "medulloblasts"<sup>7</sup> and "lymphocytes."<sup>1</sup> In our case such cells were numerous throughout the tumor and particularly tended to form vascular cuffs in the manner of ordinary lymphocytic infiltration. Glial elements, present in varying quantity, aid in establishing a classification, as mentioned before. These cells vary from spongioblasts to large and well formed astrocytes and may be numerous or few.

#### REPORT OF A CASE

*Gradual impairment of vision for three years with progressive development of headache, somnolence and vomiting. Ventriculography revealed bilateral symmetric internal hydrocephalus with complete absence of air in the third ventricle. Exploration of the third ventricle revealed a large tumor—ganglioma—which was completely removed. The patient made a good recovery.*

C. R., a white boy 9 years of age, was admitted to the Los Angeles County Hospital on Oct. 30, 1939. His mother stated that subnormal vision had first been detected when the child began school three years before. In spite of numerous pairs of glasses, the failure of vision progressed to the point that the boy was taught braille and attended a school for the blind. Frontal headache,

7. Foerster, O., and Bagel, O.: Ein Fall von Ganglioglioma des Bodens des dritten Ventrikels, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **145**:29, 1933.



although never a severe symptom, first appeared about two years before admission to the hospital and increased gradually but did not become incapacitating. In the last three months before admission to the hospital, the child manifested a marked tendency to somnolence, sleeping as many as twenty hours in the course of a day. Vomiting was frequent in the last two months; it tended to come on abruptly, often without nausea, and undoubtedly contributed to the loss of 15 pounds (6.8 Kg.) during this interval.

At no time had there been impairment of mentality or any alteration in personality. When aroused, the boy was active and, aside from the visual difficulty, presented no trouble with his gait nor any tendency to stagger.

*Examination.*—Examination revealed a rather poorly nourished but intelligent child who was able to cooperate well in neurologic testing.

Bilateral suboccipital tenderness was present together with resistance and pain on flexion of the neck. The sense of smell was intact. Visual acuity was greatly reduced, the boy being able to count fingers with the left eye at 6 feet (182.9 cm.) and with the right eye at 1 foot (30.5 cm.). Choked disks, apparently of long standing, were demonstrated in the fundi, although constant searching nystagmus made examination difficult. Left homonymous hemianopsia was thought fairly definitely to be present, and Wernicke's homonymous pupillary inaction sign appeared to be present when the right retina was tested. The left pupil was slightly greater than the right, although both were dilated and sluggish in reaction. There was considerable restriction of upward gaze.

Motor and sensory functions were intact in the extremities, and no ataxia, dysmetria or other cerebellar signs were noted. The reflexes were found to be normal throughout with equivocal bilateral Babinski signs.

Stereoroentgenograms of the skull (fig. 1 *A*) revealed the pronounced convolutional markings indicative of increased intracranial pressure of long standing. There was also some generalized separation of the cranial sutures. The pituitary fossa was enlarged, with beginning pressure erosion of the dorsum sellae turcicae.

*Diagnosis.*—The preoperative diagnostic impression was that the patient had either a craniopharyngioma (tumor or cyst of Rathke's pouch) or a neoplasm near the third ventricle, although the possibility of a midline cerebellar lesion could not be ruled out definitely.

*Operation.*—On November 9, ventriculography was carried out and demonstrated marked internal hydrocephalus, symmetric in outline with complete absence of air in the third ventricle (figs. 1 *B* and *C*). Preparations were made at once for right frontal craniotomy. With the concealed hair line incisional approach advocated by Dandy, a moderate-sized bone flap was outlined in the right frontal area and turned down without undue difficulty. The optic chiasm was inspected first to rule out the possibility of craniopharyngioma. The chiasm was found to be normal, although of a markedly prefixed type. An incision was made then through the right frontal cortex down to the dilated ventricle, interior inspection of which revealed a nubbin of tumor resting in and occluding the foramen of Monro. The foramen was gently enlarged, and a reddish vascular-appearing tumor mass was seen completely filling the anterior portion of the third ventricle. With careful blunt dissection, this mass was peeled away from the adherent walls of the ventricle and removed in toto. The wound then was given a careful toilet, with particular reference to all oozing points. The lateral ventricle was then filled with physiologic solution of sodium chloride. The lips of the cortical incision were allowed to approximate, the bone flap was returned to its correct

position, and the wound was closed in layers without drainage. Basal anesthesia induced with avertin with amylene hydrate, supplemented with ether vapor administered by nasal catheter, was used throughout the operation.

*Postoperative Course.*—The convalescent period was smooth and uneventful until the tenth postoperative day, when the patient became stuporous and a fever of 103 F. developed. Repeated tapping of the ventricular system caused a rapid fall of the temperature to normal, and the boy roused and became rational within a period of one week. The wound healed cleanly, and the patient was discharged from the hospital on December 7.

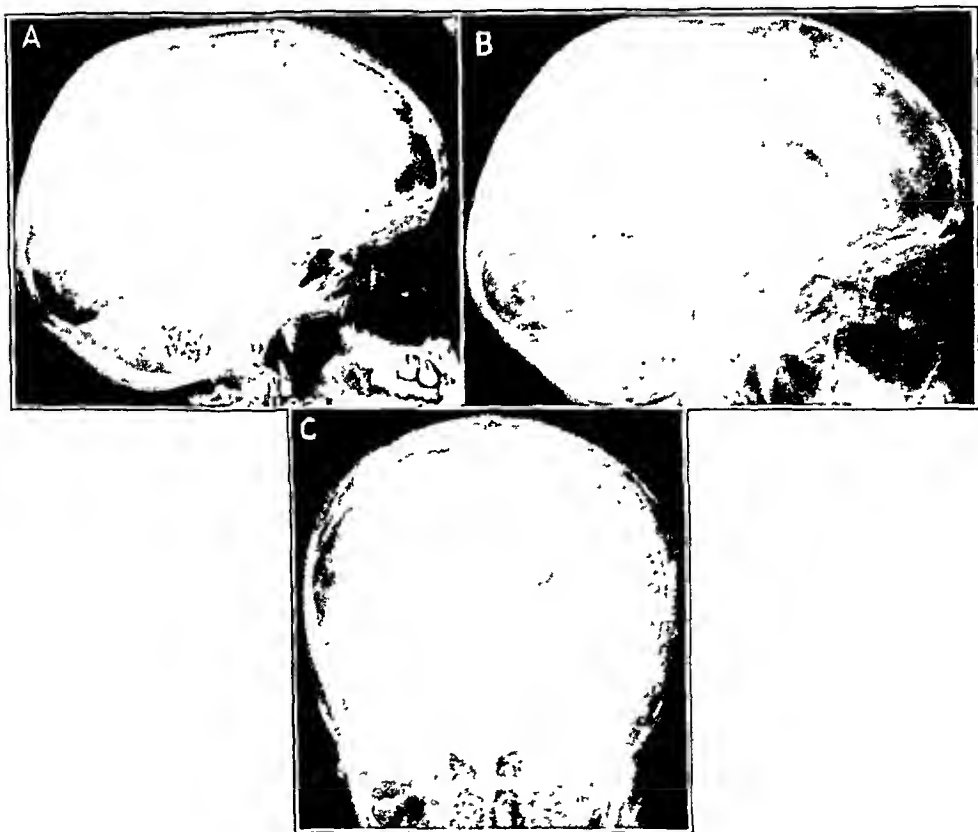


Fig. 1.—*A*, lateral roentgenogram of the skull indicating separation of sutures, increased convolutional markings and pressure erosion of the dorsum sellae turcicae. *B*, lateral ventriculogram showing marked dilatation of the ventricular system. *C*, anteroposterior ventriculogram showing symmetric internal hydrocephalus with complete absence of air in the third ventricle.

Unfortunately, this patient's vision was not improved by operation. During the year following operation, the boy was alert and active and grew about 4 inches (10.16 cm.) in height. For several months he was unable to sleep more than four or five hours per night, but this gradually lengthened to eight hours. He never showed any disturbance of water balance, but the temperature mechanism was considerably disturbed, the temperature during the day ranging from 96.4 to 97.6 F. He gained consistently in weight and strength (fig. 6).

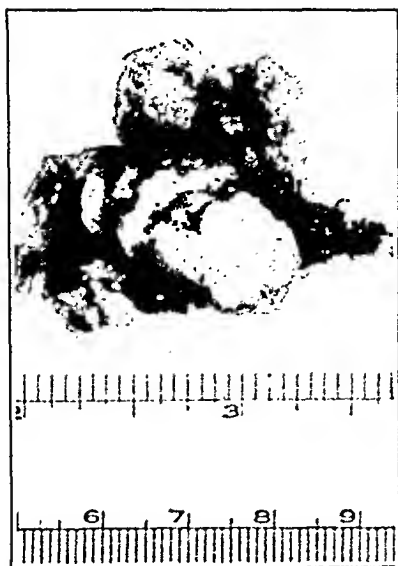


Fig. 2.—Gross specimen of ganglioglioma from the third ventricle. Weight, 7 Gm.

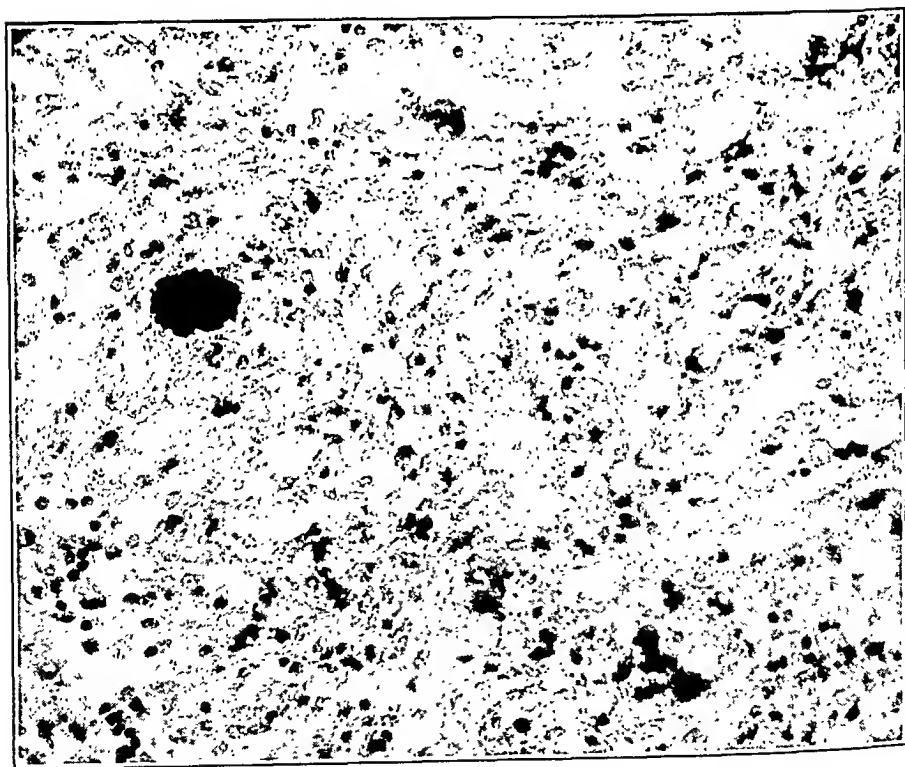


Fig. 3.—Photomicrograph of ganglioglioma showing the characteristic structure of the tumor, three ganglion cells, one with two nuclei (hematoxylin-eosin stain;  $\times 276$ ).

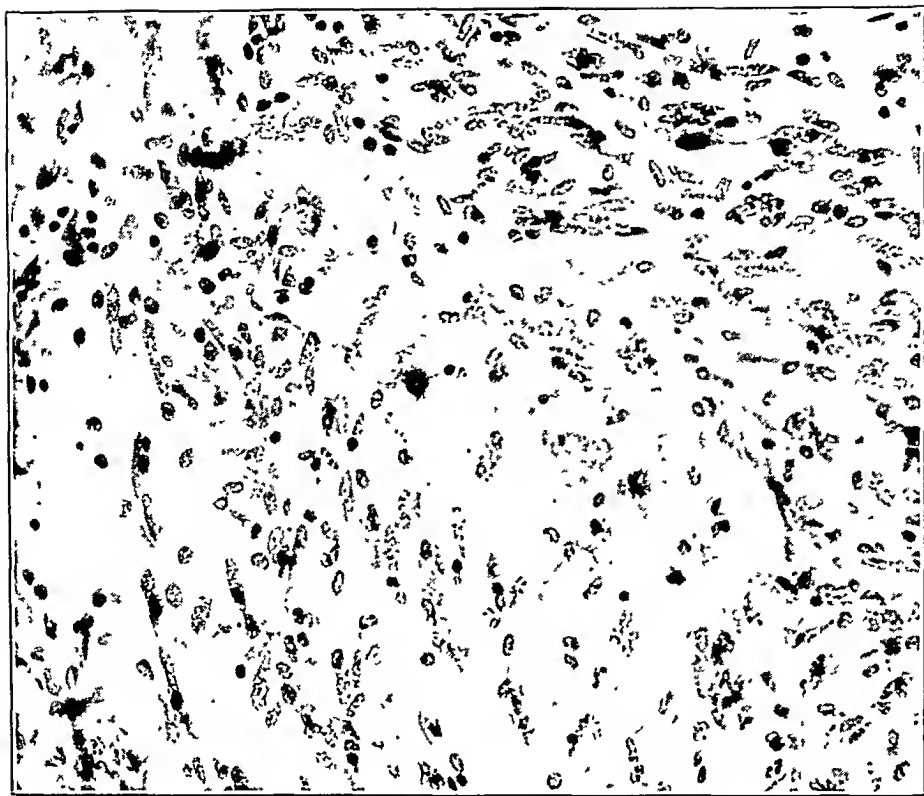


Fig. 4.—Photomicrograph of ganglioglioma (stained by cyanin method;  $\times 276$ ). Tigroid material can be fairly well made out in the center ganglion cell.

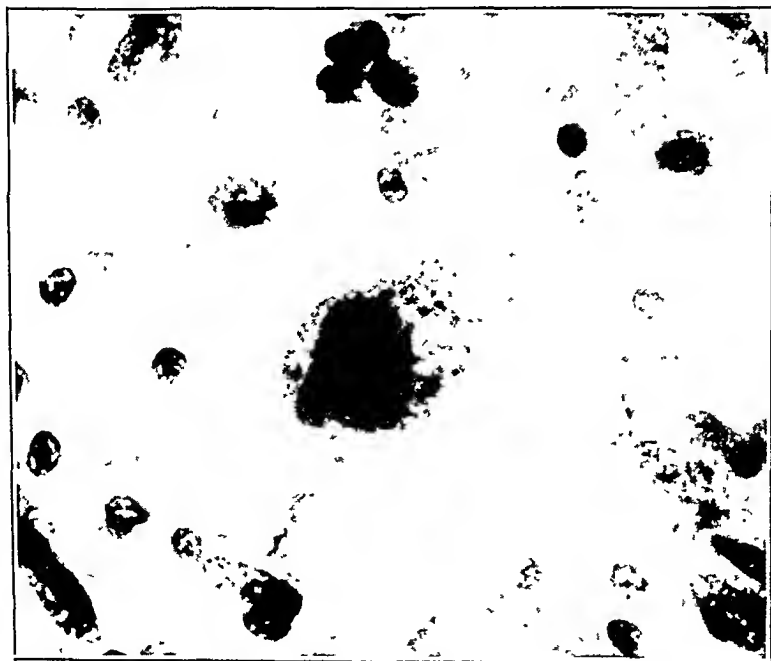


Fig. 5.—High power detail photomicrograph of nerve cells of ganglioglioma (hematoxylin-eosin stain;  $\times 800$ ).

*Pathologic Examination.*—The tumor measured approximately 3 by 4 cm. and weighed 7 Gm. (fig. 2). It was grayish pink, firm and irregularly nodular. There were a few discrete foci of hemorrhage evident on the surface, but the mass in general did not appear vascular. Histologic examination (figs. 3, 4 and 5) indicated a tumor mass made up of fibrous-like tissue in which the cells were in groups, strands or bundles. There was no definite regularity to their arrangement. A few foci of perivascular round cell infiltration were noted. Tumor giant cells were in evidence and, further, what were obviously nerve cells were found scattered throughout the growth. A section stained with the cyanin



Fig. 6.—Photograph of patient taken on April 18, 1941.

method showed a definite number of nerve cells of fairly adult type with typical vesicular nuclei; some of these had double nuclei. Many of the cells were bipolar and had nuclei elongated much like fibroblastic cells. Bielschowsky's method did not clearly demonstrate the details of the tumor, although isolated cells with threadlike processes evidently of nervous structure were seen occasionally. The stain also suggested that the great mass of the stroma forming the fibrous portion of the tumor was likewise of nervous origin. The diagnosis was ganglioglioma.

#### COMMENT

*Surgical Aspects.*—Tumors within the third ventricle present many well known obstacles to surgical treatment, and the operative results

have not always been encouraging. Before the report of Dandy<sup>8</sup> in 1921 of the successful extirpation of a colloid cyst, all third ventricle tumors had been discovered at autopsy rather than at operation. In 1933, 17 additional cases of primary neoplasm in this location were reported by Dandy,<sup>3</sup> with 2 deaths in the last 14 of the listed cases. In 1934, Masson<sup>9</sup> reported 2 cases in which removal was successful. Zimmerman and German,<sup>10</sup> Stookey,<sup>11</sup> Davidoff and Dyke<sup>12</sup> and Patterson and Leslie<sup>13</sup> also reported cases.

Postoperative deaths have been due to insurmountable damage to the essential elements in the region of the third ventricle, to postoperative intracranial hypertension and occasionally to late atresia of the cerebral aqueduct.

The majority of removable tumors are well encapsulated and, once removed, tend to recur slowly if at all. No recurrence of a colloid cyst has been reported, a fact which tends to bear out the suggestion of Sjövall,<sup>14</sup> reenforced by Zeitlin and Lichtenstein,<sup>15</sup> that these cysts are derived from remnants of the paraphysis. An estimate regarding recurrence of ganglion cell tumor in this location is, of course, not yet possible.

A frontal approach through the dilated lateral ventricle is, in the opinion of most authors, the technic of choice. Craniotomy in this location permits exploration of the chiasmal region first if suprasellar tumor is suspected; at the same operation the frontal lobe may be incised and the lateral ventricle entered. A core of frontal lobe may be excised to increase visibility if necessary. In this case the relation of the tumor and the surrounding structures was clearly outlined through the cortical incision without resort to partial frontal lobectomy. Neoplasms in the posterior portion of the third ventricle are of necessity attacked from

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8. Dandy, W. E.: Diagnosis, Localization, and Removal of Tumors of the Third Ventricle, *Bull. Johns Hopkins Hosp.* **33**:188, 1922.

9. Masson, C. G.: Complete Removal of Two Tumors of the Third Ventricle with Recovery, *Arch. Surg.* **28**:527 (March) 1934.

10. Zimmerman, H. M., and German, W. J.: Colloid Tumors of the Third Ventricle, *Arch. Neurol. & Psychiat.* **30**:309 (Aug.) 1933.

11. Stookey, B.: Intermittent Obstruction of the Foramen of Monro by Neuro-Epithelial Cysts of the Third Ventricle, *Bull. Neurol. Inst. New York* **3**:446, 1934.

12. Davidoff, L. M., and Dyke, C. M.: Congenital Tumors in the Rostral Portion of the Third Ventricle, *Bull. Neurol. Inst. New York* **4**:221, 1935.

13. Patterson, J. E., and Leslie, M.: Colloid Cyst of the Third Ventricle of the Brain: Report of a Case Operated on with Recovery, *Brit. M. J.* **1**:920, 1935.

14. Sjövall, E.: Ueber eine Ependymcyste embryonalen Charakters (Paraphyse?) im dritten Hirnventrikel mit tödlichen Ausgang, *Beitr. z. path. Anat. u. z. allg. Path.* **47**:248, 1909.

15. Zeitlin, H., and Lichtenstein, B. W.: Cystic Tumor of the Third Ventricle Containing Colloid Material, *Arch. Neurol. & Psychiat.* **38**:268 (Aug.) 1937.

above through the corpus callosum. This approach is favored by Dandy unless the tumor is located at the anterior extremity of the ventricle.

*Symptoms of Third Ventricle Tumors.*—The various symptoms and signs which may be produced by tumors encroaching on the third ventricle have been the subject of considerable study. An excellent treatise on this subject was presented by Fulton and Bailey<sup>16</sup> in 1929. They cited the opinions of many workers before them (Weisenberg, Jumentie and Chausseblanche, Courtney and others) and reported 5 cases of their own, 4 with necropsy. The symptomatology was reviewed by Oldberg and Eisenhardt<sup>17</sup> in a series of 22 cases which they described in 1938 and by Nielsen and Raney<sup>18</sup> a year later. All of these writers noted a fairly constant symptom complex in the presence of third ventricle neoplasms.

The features described are: (1) hypersomnia, a frequent finding, felt to be due to encroachment on the posterior portion of the ventricle near the mouth of the cerebral aqueduct; (2) psychic disturbances, with loss of personality and memory, outbursts of anger, melancholy and mental dulness; (3) vegetative symptoms, including disturbances in temperature regulation, adiposity and genital dystrophy, circulatory dysfunction, such as blood pressure variations and "diencephalic epilepsy" (4) thalamic symptoms—painful hypesthesia, central pain; (5) pyramidal signs, such as facial weakness and Babinski signs; (6) "cerebellar" signs, secondary to pressure on the frontocerebellar association tracts.

Acute headache, dizziness and fainting with change in position of the head have been recorded, but these are frequently not present and may be seen with tumors in other locations. Symptoms and signs, such as uncinat fits, visual field defects and disturbances of pupillary and extraocular motility, have been observed.

Our patient's somnolence was an outstanding complaint, but it is true that he had intracranial hypertension and hydrocephalus, making the evaluation of this symptom uncertain. He presented evidence of impairment in the right optic tract and considerable restriction of upward gaze, both of which were consistent with the diagnosis of a third ventricle neoplasm; but no other specific findings were present and at no time were there any aberrations of the mental status.

It is recognized that continued study and observation of cases presenting third ventricle tumors will lead to the diagnosis of a goodly percentage on the basis of symptoms and neurologic findings before

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16. Fulton, J., and Bailey, P.: A Contribution to the Study of Third Ventricle Tumors: Their Diagnosis and Relation to Pathological Sleep, *J. Nerv. & Ment. Dis.* **69**:1, 145 and 261, 1929.

17. Oldberg, E., and Eisenhardt, L.: The Neurological Diagnosis of Tumors of the Third Ventricle, *Tr. Am. Neurol. A.* **64**:33, 1938.

18. Nielsen, J. M., and Raney, R. B.: Symptomatology of Tumors of the Third Ventricle, *Bull. Los Angeles Neurol. Soc.* **4**:1, 1939.

ventriculography is performed. At present, however, one hesitates to proceed with craniotomy in even the most classic case without the localizing benefit of ventriculographic study.

#### SUMMARY AND CONCLUSIONS

A case of a third ventricle tumor (ganglioglioma) with operative removal and clinical recovery is reported.

The most common site of origin of these ganglion cell tumors appears to be the floor of the third ventricle.

No definite clinical syndrome of a neoplasm in the third ventricle can be accurately described.

Ventriculography is indicated in every case in which the presence of the condition is suspected.

The chief operative procedures involving the removal of a third ventricle tumor are described.



# INFLUENCE OF ABDOMINAL BINDERS ON LUNG VOLUME AND PULMONARY DYNAMICS

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Abdominal binders are used routinely after abdominal operations, and we have therefore studied the changes in pulmonary function caused by their application. The lung volume, its subdivisions and related aspects of pulmonary function have been measured before and after the application of abdominal swathes, and the possible relation of the findings to postoperative pulmonary complications has been considered.

## MATERIAL AND METHODS

Studies were made on 8 subjects. Six subjects (1 to 6) were normal and ranged in age from 20 to 47 years; 3 (1, 5 and 6) were men. The other 2 subjects (7 and 8), respectively 53 and 59 years old, had pulmonary congestion due to chronic myocardial insufficiency; 1 (7) was a man. The method of Christie,<sup>1</sup> slightly modified,<sup>2</sup> was used, all measurements on normal subjects being made with the subject recumbent. In the patients with pulmonary congestion, the studies were made with the subject sitting at an angle of 80 degrees to the horizontal, since these persons could not tolerate abdominal binders when recumbent. Measurements were made both before and after the application of the binders, which extended from the symphysis pubis to just below the xiphoid process. The binders were applied with varying degrees of tightness to different subjects (table).

## OBSERVATIONS

The volume of the functional residual air, composed of the reserve and residual airs, decreased in all the normal subjects after application of the binder, the decreases ranging from 1.1 and 6.3 per cent in those with snug binders to 15.0 and 20.4 per cent in those with tight binders; in the 2 patients with pulmonary congestion, moderately tight binders caused decreases in the functional residual air of 6.8 and 11.5 per cent,

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1. Christie, R. V.: The Lung Volume and Its Subdivisions: I. Method of Measurement, *J. Clin. Investigation* **11**:1099, 1932.

2. Iglauder, A., and Altschule, M. D.: The Effect of Arterial and Venous Constriction Induced by Paredrine (p-Hydroxy- $\alpha$ -Methylphenylethylamine Hydrobromide) on the Lung Capacity and Its Subdivisions, *Am. J. M. Sc.* **201**:664, 1941.

as compared with 9.4 and 9.5 per cent in the normal subjects (table and chart).

The volume of the reserve air, one component of the functional residual air, decreased in all the normal subjects after application of the binder, the decreases ranging from 5.6 and 11.7 per cent in those with snug binders to 33.3 and 50.4 per cent in those with tight binders. In the 2 patients with pulmonary congestion, moderately tight binders

*Data on the Influence of Abdominal Binders on Lung Volume and Pulmonary Dynamics in Eight Subjects*

Subject	Functional Residual Air, Cc.	Reserve Air, Cc.	Residual Air, Cc.	Complemental Air, Cc.	Vital Capacity, Cc.	Total Capacity, Cc.	Tidal Air, Cc.	Respiratory Rate	Respiratory Minute Volume, Liters	Oxygen Consumption, Cc. per Minute	Comment
1	2,470 2,315	950 835	1,520 1,480	3,170 3,210	4,120 4,045	5,640 5,525	435 385	16 21	6 96 8 10	270 209	No binder Snug binder
2	1,685 1,665	715 675	970 990	2,500 2,500	3,215 3,175	3,985 3,850	515 475	7 8	3 61 6 80	188 176	No binder Snug binder
3	1,520 1,375	475 355	1,045 1,020	2,540 2,500	3,015 2,835	4,060 3,875	715 535	8 11	5 72 5 89	242 200	No binder Moderately tight binder
4	2,345 2,125	515 395	1,830 1,730	1,745 1,625	2,260 2,020	4,090 3,750	445 525	13 14	5 25 7 35	207 217	No binder Moderately tight binder
5	2,200 1,870	360 240	1,840 1,630	3,210 2,660	3,570 2,900	4,040 3,530	535 475	16 18	8 56 8 55	231 240	No binder Tight binder
6	1,835 1,460	555 280	1,280 1,180	3,410 2,740	3,965 3,020	5,245 4,200	475 405	15 18	7 13 7 29	286 268	No binder Tight binder
7*	3,310 3,085	710 520	2,600 2,565	2,060 1,710	2,770 2,230	5,370 4,795	595 575	16 21	9 90 11 80	293 299	No binder Moderately tight binder
8*	1,740 1,540	320 80	1,420 1,460	830 790	1,150 870	2,570 2,330	415 435	24 26	10 00 11 30	224 213	No binder Moderately tight binder

\* Subject had pulmonary congestion due to chronic myocardial insufficiency.

caused decreases in the reserve air of 26.8 and 75.0 per cent as compared with 23.3 and 25.3 per cent in the normal subjects (table and chart).

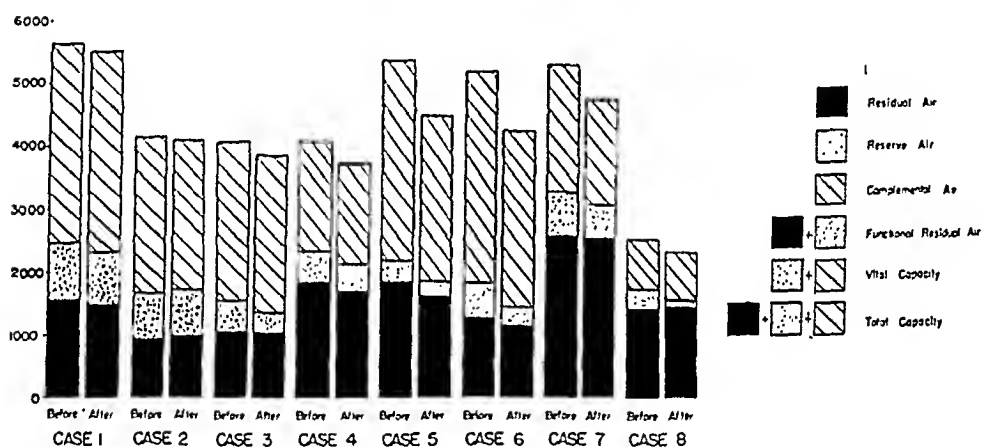
The volume of the residual air, the other component of the functional residual air, was unchanged after the application of snug or moderately tight binders to normal subjects and to those with pulmonary congestion. Tight binders caused slight decreases in residual air, i. e., 7.8 and 11.4 per cent, respectively, in the 2 subjects to whom they were applied (table and chart).

The volume of the complemental air was unchanged or slightly increased after the application of snug binders. Moderately tight and tight binders caused respective decreases in the normal subjects of 1.6 and 6.9 per cent and 17.1 and 19.6 per cent. Moderately tight binders

caused a decrease in complementary air of 4.8 and 17.0 per cent in the 2 patients with pulmonary congestion (table and chart).

The volume of the vital capacity decreased in all the normal subjects after application of the binder, the decreases ranging from 1.2 and 2.1 per cent in those with snug binders to 18.8 and 23.8 per cent in those with tight binders. In the 2 patients with pulmonary congestion moderately tight binders caused decreases in vital capacity of 19.5 and 4.3 per cent, as compared with only 5.3 and 10.6 per cent in the normal subjects (table and chart).

The volume of the total pulmonary capacity decreased in all the normal subjects after application of the binders, the decreases ranging from 2.0 and 3.4 per cent in those with snug binders to 12.6 and 19.9 per cent in those with tight binders. In the 2 patients with pulmonary



Changes in pulmonary function caused by the application of abdominal binders.

congestion moderately tight binders caused decreases in total capacity of 10.9 and 17.1 per cent, as compared with only 4.6 and 8.3 per cent in the normal subjects (table and chart).

The respiratory rate increased in all cases after application of the binder; the tidal volume decreased in 5 of the 6 normal subjects and 1 of the 2 patients with pulmonary congestion. The degree of tightness of the binder did not influence the amount of change in these measurements. The respiratory minute volume was unchanged in 4 of the 6 normal subjects, increasing in the other 2 and in both patients with pulmonary congestion. No changes in oxygen consumption occurred (table).

#### COMMENT

McMichael and McGibbon<sup>3</sup> showed that abdominal binders cause a cephalad shift in the position of the diaphragm. This results in

3. McMichael, J., and McGibbon, J. P.: Postural Changes in the Lung Volume, Clin. Sc. 4:175, 1939.

decreases in functional residual and reserve air, as the data of the present study show, varying with the degree of abdominal constriction. A tight abdominal binder, i. e., as tight as the usual postoperative binder, diminishes the functional residual air by 15 or 20 per cent. This implies a corresponding degree of pulmonary collapse and suggests that binders favor the occurrence of postoperative atelectasis. The decreases in functional residual air due to tight swaths also indicate that abdominal constriction causes a decrease in the negativity of the intrapleural pressure. In the present study it was found that tight abdominal binders cause decreases in functional residual air of 330 to 375 cc.; Christie and MacIntosh<sup>4</sup> found that the negativity of the intrapleural pressure decreased 2 to 3 cm. of water when the functional residual air diminished 200 to 350 cc. Decreased negativity of intrapleural pressure impedes peripheral venous return, as has been discussed elsewhere.<sup>5</sup> It has been shown also that abdominal binders may impede venous return from the legs by compressing the great veins of the abdomen.<sup>6</sup> These factors are clearly of importance as contributory causes in the genesis of postoperative shock and phlebitis.

The decrease in complemental air resulting from abdominal constriction also is of clinical significance. Many years ago Haldane, Meakins and Priestley<sup>7</sup> showed that prolonged maintenance of restriction of the tidal air, a portion of the complemental air, by means of abdominal or chest binders or other devices, results in fatigue of the respiratory center and anoxemia. This may be manifested by various respiratory arrhythmias, including Cheyne-Stokes respiration; the occurrence of such arrhythmias was noted in the present study.

It is clear that the application of tight abdominal binders, as practiced routinely after abdominal operations, favors atelectasis, has deleterious effects on respiratory function and impedes venous return. It is worthy of note that patients with pulmonary congestion show evidences, both by the measurements of this study and by clinical observation, of greatly increased dyspnea and a greater degree of respiratory embarrassment than normal subjects as a consequence of abdominal constriction.

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4. Christie, R. V., and MacIntosh, C. A.: The Measurement of the Intrapleural Pressure in Man and Its Significance, *J. Clin. Investigation* **13**:279, 1934.

5. Altschule, M. D., and Zamcheck, N.: Significance of Changes in the Subdivisions of the Lung Volume in the Trendelenburg Position, *Surg., Gynec. & Obst.*, to be published.

6. Davis, D., and Gilman, S.: Factors Causing Increase in Venous Pressure of the Lower Extremities During Abdominal Operations, *J. Clin. Investigation* **20**:443, 1941.

7. Haldane, J. S.; Meakins, J. C., and Priestley, J. G.: The Effects of Shallow Breathing, *J. Physiol.* **52**:433, 1919.

## SUMMARY AND CONCLUSIONS

The lung volume, its subdivisions and related aspects of pulmonary function have been studied in normal subjects and patients with pulmonary congestion before and after the application of abdominal swathes of varying degrees of tightness.

Decreases in functional residual air, varying with the degree of constriction, result from the application of abdominal binders. These changes indicate that atelectasis may occur as a consequence of abdominal constriction. Impairment of respiratory efficiency and venous return result from the decreased negativity of intrapleural pressure implied by diminution in the functional residual air.

Tight binders reduce the complemental air; this limitation of tidal expansion may give rise to fatigue of the respiratory center and anoxemia, resulting in respiratory arrhythmias.

# SYMPATHECTOMY OF THE UPPER EXTREMITY

EVIDENCE THAT ONLY THE SECOND DORSAL GANGLION NEED BE  
REMOVED FOR COMPLETE SYMPATHECTOMY

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For a long time the standard sympathectomy of the upper extremity consisted of cervicodorsal ganglionectomy—removal of the inferior cervical and first and second dorsal ganglions.

In 1934, Freeman, Smithwick and White<sup>1</sup> began a series of studies which led to the employment of preganglionic sympathectomy in the treatment of Raynaud's disease of the upper extremity.<sup>2</sup> This was based on the proposition that the standard cervicodorsal ganglionectomy being postganglionic renders the vessels of the extremity more sensitive to circulating epinephrine. In 1936, Smithwick<sup>3</sup> proposed a preganglionic sympathectomy to be carried out as follows: The dorsal sympathetic chain is severed below the third dorsal ganglion. All rami to and from the second and third ganglions are severed, and the proximal end

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1. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenaline and to Adrenal Secretion Resulting from Insulin Hypoglycemia, *Am. J. Physiol.* **107**:529, 1934. Smithwick, R. H.; Freeman, N. E., and White, J. C.: Effect of Epinephrine on the Sympathectomized Human Extremity: An Additional Cause of Failure of Operations for Raynaud's Disease, *Arch. Surg.* **29**:759 (Nov.) 1934.

2. J. F. Fulton (*Physiology of the Nervous System*, New York, Oxford University Press, 1938, p. 220) pointed out that W. K. Livingston (*The Clinical Aspects of Visceral Neurology*, Springfield, Ill., Charles C. Thomas, Publisher, 1935) was the first to do a modified form of preganglionic sympathectomy to the upper extremity. He was prompted, however, by the belief that removal of the inferior cervical and upper two dorsal ganglions does not constitute a complete sympathectomy to the upper extremity and apparently did not have epinephrine sensitivity of the sympathectomized vessel in mind.

3. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity: A Preliminary Report, *Ann. Surg.* **104**:339-350, 1936; The Value of Sympathectomy in the Treatment of Vascular Disease, *New England J. Med.* **216**:141-150, 1937.

of the chain is sutured into the muscles of the back to insure against regeneration. To insure complete ramisectomy, segments of the second and third intercostal nerves are removed up to their emergence from the dura.

In 1935, Telford<sup>4</sup> proposed that preganglionic sympathectomy be done by severing the white rami of the second and third intercostal nerves and severing the sympathetic chain below the third dorsal ganglion.

In these operations all rami to and from the first intercostal nerve are left unmolested, and hence the completeness of sympathectomy is contingent on the absence of preganglionic fibers to the upper extremity in the first thoracic anterior root.

Kuntz<sup>5</sup> demonstrated as early as 1927 that the first thoracic nerve sends a white ramus into the stellate ganglion. He pointed out that since the first thoracic nerve contributes largely to both the median and the ulnar nerves, the sympathetic fibers contained in it (including those which enter via the ramus from the second thoracic nerve, whenever this ramus is present) are relatively widely distributed to blood vessels and other tissues in the upper extremity. In 1938, Kuntz, Alexander and Furcolo<sup>6</sup> demonstrated by histologic methods that the white ramus of the first thoracic nerve is important in supplying sympathetic nerves to the upper extremity. They stated:

. . . If the distribution of preganglionic fibers of the first thoracic nerve in man corresponds to the distribution of these fibers in the cat and the dog, sympathetic denervation of the blood vessels in the upper extremity in man obviously cannot be accomplished by any operative procedure which leaves intact the first thoracic nerve with its communicating ramus and the inferior cervical ganglion with the gray communicating rami which connect it with the nerves which make up the brachial plexus.

Kuntz further showed that stimulation of the ventral root of the first, the second or the third thoracic nerve results in activation of sweat glands in the paw pads and constriction of cutaneous vessels of the foot. He concluded that:

. . . Both the anatomic and the physiologic findings indicate that preganglionic components of the first thoracic nerve play an important role in the sympathetic innervation of the upper extremity both with regard to the sweat glands and the vascular musculature.

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4. Telford, E. D.: The Technique of Sympathectomy, *Brit. J. Surg.* **23**:448-450, 1935; Sympathetic Denervation of the Upper Extremity, *Lancet* **1**:70-72, 1938.

5. Kuntz, A.: Distribution of the Sympathetic Rami to the Brachial Plexus: Its Relation to Sympathectomy Affecting the Upper Extremity, *Arch. Surg.* **15**: 871-877 (Dec.) 1927.

6. Kuntz, A.; Alexander, W. F., and Furcolo, C. L.: Complete Sympathetic Denervation of the Upper Extremity, *Ann. Surg.* **107**:25-31, 1938.

The results of Kuntz's work were based on the findings in animals and do not agree with the findings in man.

Whether and to what extent the type of sympathectomy proposed by Smithwick and by Telford is a preganglionic sympathectomy and whether this type of sympathectomy solves the problem of Raynaud's disease of the upper extremity are matters that will be reserved for further publications. It is our purpose at present to show only that the first thoracic anterior root in man contains no sympathetic fibers to the upper extremity and that hence the operation as performed by Smithwick and by Telford is a complete sympathectomy so far as central connections are concerned. Furthermore, since Smithwick based his con-



Fig. 1 (case 1).—Patient after thermoregulatory sweating test. There was complete anhidrosis on the right down to the skin level of the third dorsal segment and including the right upper extremity. Only the second dorsal sympathetic ganglion was removed.

clusions of completeness of sympathectomy on the psychogalvanic reflex,<sup>7</sup> we feel that it is of value to report our results based on another method—Minor's starch-iodine sweating test.<sup>8</sup>

#### REPORT OF CASES

CASE 1.—N. B., a white woman 42 years of age, had gastric crises of tabes dorsalis.

7. Smithwick, R. H.: Surgical Intervention on the Sympathetic Nervous System for Peripheral Vascular Disease, *Arch. Surg.* **40**:286-306 (Feb.) 1940.

8. Minor, V.: Eines neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung, *Deutsche Ztschr. f. Nervenhe.* **40**:286-306, 1940.



*Operation.*—Bilateral anterior chordotomy at the second thoracic segment was done on July 6, 1940. With the patient's permission, the second dorsal sympathetic ganglion only was removed on the right. She was relieved of the pain of gastric crises.

*Thermoregulatory Sweating Test.*—This test was repeated several times with the same result. The photograph shown in figure 1 was taken on Sept. 16, 1940. The zone of anhidrosis on the right was complete and equivalent to that which results from the standard cervicodorsal ganglionectomy (removal of the inferior cervical and upper two dorsal ganglions).



Fig. 2 (case 2).—Patient after thermoregulatory sweating test. There was complete anhidrosis down to the skin level of the third dorsal segment on the left and the fourth dorsal segment on the right. On the left, the inferior cervical and upper two dorsal ganglions were removed. On the right, all rami to and from the second and third ganglions were severed, and the chain was sectioned below the third ganglion.

CASE 2.—E. V., a white woman 45 years of age, had Raynaud's disease.

*Operation.*—On Aug. 19, 1940, on the right, the sympathetic chain was sectioned below the third dorsal ganglion. All rami to and from the second and third dorsal ganglions were severed, and the proximal end of the chain was sutured to the nearest muscle of the back. The rami to and from the inferior cervical and first dorsal ganglions were not molested. On the left, the inferior cervical and upper two dorsal ganglions were removed.

*Thermoregulatory Sweating Test.*—Anhidrosis was complete down to the third dorsal segment on the left and down to the fourth dorsal segment on the right (fig. 2).

CASE 3.—M. G., a white girl 22 years of age, suffered from migraine.

*Operation.*—On Oct. 2, 1940, on the right side, the sympathetic chain was sectioned below the third dorsal ganglion. Segments of the second and third

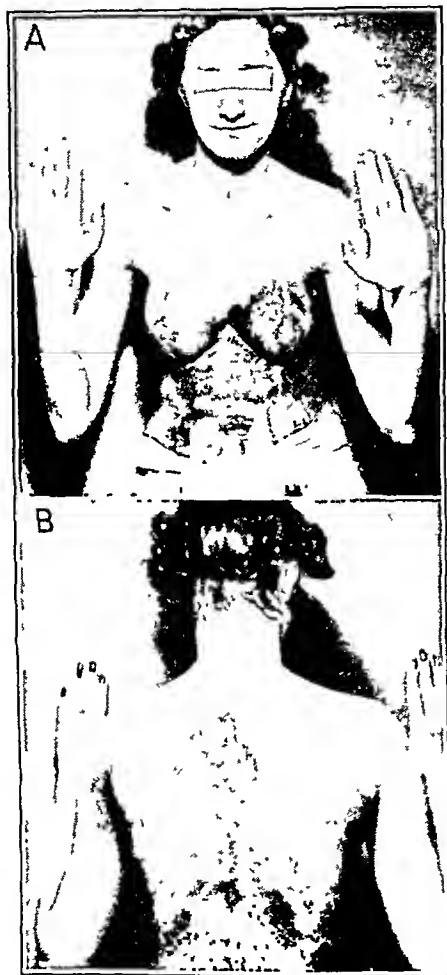


Fig. 3 (case 3).—Patient after thermoregulatory sweating test. There was complete anhidrosis down to the skin level of the third dorsal segment on the left and the fourth dorsal segment on the right. On the left, all rami to and from the second dorsal ganglion were severed, and the chain was sectioned below the second ganglion. On the right, segments of the second and third intercostal nerves were removed proximal to their rami, and the chain was sectioned below the third ganglion. *A*, front view; *B*, back view.

intercostal nerves were removed from the sympathetic chain almost to the spinal dura so that the sensory ganglions were included. All rami were left intact, and

the proximal cut end of the chain was sutured to the nearest muscle of the back. On the left side, all rami to the second dorsal ganglion were severed, a segment of the second intercostal nerve was removed, and the chain was sectioned below the second ganglion.

*Thermoregulatory Sweating Test.*—This test was repeated several times with the same result. The photograph shown in figure 3 was taken on March 13, 1941.

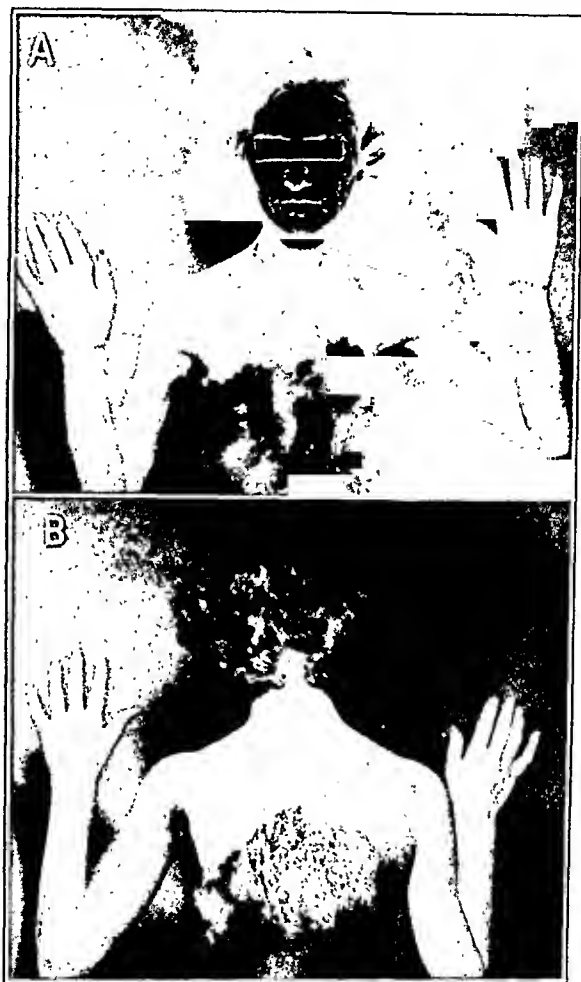


Fig. 4 (case 4).—Patient after thermoregulatory sweating test. There was complete anhidrosis down to the skin level of the third dorsal segment on the left and the fourth dorsal segment on the right. On the left, the second dorsal ganglion only was removed. On the right, all rami to and from the second and third ganglions were severed, and the chain was sectioned below the third ganglion. *A*, front view; *B*, back view.

Anhidrosis was complete down to the third dorsal segment on the left and down to the fourth dorsal segment on the right.

The influence of the sympathectomy on the migraine was disappointing.

CASE 4.—M. S., a white woman 26 years of age, had Raynaud's disease.

*Operation.*—On Jan. 4, 1941, on the right, all rami to and from the second and third dorsal ganglions were severed; the chain was sectioned below the third ganglion, and the cut end of the proximal chain was sutured to the nearest muscle of the back. On the left, the second dorsal ganglion only was removed.

*Thermoregulatory Sweating Test.*—Anhidrosis was complete down to the third dorsal segment on the left and down to the fourth dorsal segment on the right (fig. 4).



Fig. 5 (case 5).—Patient after thermoregulatory sweating test. There was complete anhidrosis down to the skin level of the third dorsal segment on the left. Only the second dorsal ganglion was removed on the left.

CASE 5.—R. R., a white man 38 years of age, had amputation stump pain on the left and pain in the phantom hand.

*Operation.*—The injection of procaine hydrochloride about the upper dorsal ganglions on the left markedly relieved the pain. On Nov. 19, 1941, the second dorsal ganglion only was removed on the left.

*Thermoregulatory Sweating Test.*—Anhidrosis was complete down to the third dorsal segment on the left (fig. 5).

## COMMENT

Although this is not the place to discuss results other than those implied by the title, we would like to say that the relief of pain in case 5 has been complete to the time of writing (two months). This implies that relief of "sympathetic" pain in parts other than viscera is due to interruption of the efferent sympathetic supply as opposed to interruption of sympathetic afferents. We are dispelling the doubt we formerly entertained in this connection.

The amputation stump, which felt cool before operation, became 3 degrees warmer than a corresponding place on the right forearm. This increase in warmth was far greater than we had ever obtained on this part of the intact forearm after sympathectomy. Such a result has its implications in relation to the fact that only the terminal ends of the extremities become warmer after sympathectomy.<sup>9</sup>

*Capillary Flushing Test.*—We <sup>9a</sup> have previously shown that sympathectomy abolishes the capillary flushing that is caused by severe heating. The flushing is centrally controlled, and the fibers which subserve the capillary dilatation course through anterior roots and the thoracolumbar sympathetic chain. They parallel the course of sweat fibers.

In all of the patients described, the abolition of centrally controlled capillary dilatation coincided as nearly as we could tell with the anhidrosis. In cases 1 and 5, in which the sympathectomy was unilateral and only the second dorsal ganglion was removed, this fact was made obvious. The demarcation between the flushed and unflushed zones on the face was as marked after heating the body as it is after unilateral cervicodorsal ganglionectomy.

*Epinephrine Test.*—Repeated measurements of finger temperature in cases 2, 3 and 4 indicated no essential differences on the two sides. Skin temperatures were followed in the usual way while epinephrine was injected intravenously (1:250,000 at 40 to 60 drops per minute). The drop in temperature of the fingers was essentially the same on the two sides. The studies were made after time for degeneration had elapsed. The details of these studies are reserved for an appropriate publication, but they have a bearing on what we feel to be true—that removal of only the second dorsal ganglion results in the maximal effects and benefits that can be derived from sympathectomy of the upper extremity.

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9. Hyndman, O. R., and Wolkin, J.: (a) The Autonomic Mechanism of Heat Conservation and Dissipation: I. Effects of Heating the Body; Evidence for the Existence of Capillary Dilator Nerves in Anterior Roots, *Am. Heart J.* **22**:289-304, 1941; (b) Effects of Cooling the Body: A Comparison of Peripheral and Central Vasomotor Responses to Cold, *ibid.* **23**:43-58, 1942.

In all of the 5 cases reported, the rami to and from the inferior cervical and first dorsal ganglions were left intact. Hence all pre-ganglionic fibers which course in the first thoracic anterior root were preserved. Nevertheless, thermoregulatory anhidrosis and abolition of centrally controlled capillary dilatation were as complete as they are when the inferior cervical and first dorsal ganglions are included in the sympathectomy. Hence it can be deduced that there are no preganglionic sympathetic fibers in the first thoracic anterior root, the connections of which are destined for the sweat glands or capillaries.<sup>10</sup> The statement could probably be made to include all skin structures and deeper vessels of the parts under consideration.

In the second case, a standard cervicodorsal ganglionectomy was done on the left, while on the right, the inferior cervical and first dorsal ganglions were left intact. After the operation, the left upper extremity was painful for several months. The burning pain appeared to be similar to that in peripheral neuritis and was so distressing that it offset the good results due to sympathectomy. In our experience, we have frequently encountered a pain of this type after cervicodorsal ganglionectomy, and we believe it to be a traumatic neuritis or neuralgia referable to the manipulation of the cords of the brachial plexus when the stellate ganglion is removed. We<sup>11</sup> called attention to this in a previous report and pointed out that Adson<sup>12</sup> had experience with the same complication. The patient's right upper extremity was comfortable and devoid of pain so that the result in that extremity was satisfactory to the patient and to us.

It may well be that the poor results from the treatment of Raynaud's disease of the upper extremity by cervicodorsal sympathectomy and the better results which have followed the Smithwick operation are referable to this complication which attends the former method rather than being referable to the difference between preganglionic and postganglionic sympathectomy. The complication naturally does not follow a lumbar ganglionectomy for the lower extremity. We have recently submitted

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10. The only possible arrangement that could make this statement untrue is one in which supposed preganglionic fibers in the first thoracic root coursed downward in the sympathetic chain to synapse with postganglionic neurons below the third dorsal ganglion and that the latter coursed up the chain again to emerge in the gray rami of the inferior cervical and first dorsal ganglions. Such an arrangement is hardly likely.

11. Hyndman, O. R., and Wolk, J.: Raynaud's Disease: A Review of Its Mechanism; Evidence That It Is Primarily a Vascular Disease, *Am. Heart J.* **23**:535-554, 1942.

12. Brown, G. E., and Adson, A. W.: Physiologic Effects of Thoracic and of Lumbar Sympathetic Ganglionectomy or Section of the Trunk, *Arch. Neurol. & Psychiat.* **22**:322-357 (Aug.) 1929.

evidence<sup>11</sup> which supports Lewis' contention that Raynaud's disease is primarily a vascular abnormality and not primarily an abnormality of the sympathetic system. Hence while sympathectomy is beneficial, it does not effect a cure of the abnormality.

In any case, we feel that these and other studies lead definitely to the conclusion that it is not necessary to remove the stellate ganglion (inferior cervical and first dorsal ganglions) to effect a complete efferent sympathectomy to the face and the upper extremity. The additional procedure is superfluous and often fraught with a complicating pain that is probably a traumatic neuralgia. In dealing with sympathetic pain syndromes (amputation stump pain, causalgia and angina pectoris), we are developing the conviction that any relief of pain from sympathectomy, insofar as the extremities are concerned, is due to the interruption of efferent sympathetic pathways.

Our results have not convinced us that the more elaborate preganglionic sympathectomy<sup>13</sup> as proposed by Smithwick is more beneficial than removal of only the second dorsal ganglion, and hence we suggest that a removal of only the second ganglion should give optimal results with a minimal amount of operation and minimal complications.

The second anterior thoracic root contains many preganglionic fibers to the upper extremity, and hence for complete sympathectomy it is necessary that all connections from the second thoracic nerve be severed. We<sup>14</sup> reported 2 cases of extensive anterior rhizotomy in which the second thoracic roots were left intact. Thermoregulatory sweating on the upper extremities was abundant. In fact, in 1 case, sweating was abundant down to the skin level of the sixth dorsal segment. Recently, Atlas<sup>15</sup> reported a case in which the second dorsal ganglion was removed on the right side and the third dorsal ganglion on the left. The right hand became anhidrotic, while the left continued to sweat.

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13. And indeed to just what extent the Smithwick operation is a preganglionic sympathectomy remains to be proved. Both clinical (Hyndman and Wolkin<sup>14</sup>) and experimental studies (Geohegan, W. A., and others: *The Spinal Origin of the Preganglionic Fibers to the Limbs in the Cat and Monkey*, *Am. J. Physiol.* **135**: 324-329, 1942) have shown that preganglionic sweat fibers the connections of which are destined for the upper extremity course through anterior roots below as well as above the fifth dorsal segment and as far down as the eleventh dorsal segment. It is likely that many of their synapses with postganglionic neurons occur in ganglia below the third dorsal.

14. Hyndman, O. R., and Wolkin, J.: *Sweat Mechanism in Man: Study of Distribution of Sweat Fibers from the Sympathetic Ganglia, Spinal Roots, Spinal Cord and Common Carotid Artery*, *Arch. Neurol. & Psychiat.* **45**:446-467 (March) 1941.

15. Atlas, L. N.: *The Role of the Second Thoracic Spinal Segment in the Preganglionic Sympathetic Innervation of the Human Hand: Surgical Implications*, *Ann. Surg.* **114**:456-461, 1941.

## CONCLUSIONS

Removal of only the second dorsal sympathetic ganglion results in as complete a sympathectomy insofar as central connections are concerned as does removal of the inferior cervical and upper two dorsal ganglions (the standard cervicodorsal ganglionectomy).

Hence no sympathetic fibers which supply the skin structures of the face and the upper extremity reside in the first anterior thoracic root in man. Operative removal of only the second dorsal ganglion is a simple procedure which insures a complete sympathectomy to the upper extremity and optimal physiologic results that can be attributed to efferent sympathectomy.



# INTERMITTENT VOLVULUS OF THE MOBILE CECUM

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Partial volvulus of a mobile cecocolon is a definite but rarely suspected cause of intermittent pain in the right lower quadrant of the abdomen. Usually the diagnosis of this disorder is not established until an obvious attack of intestinal obstruction occurs and laparotomy demonstrates the cecal volvulus. It then becomes evident that the chronic symptoms which antedated the acute episode were occasioned by similar but partial and transitory torsion of the mobile cecocolon. The purpose of the present report is to demonstrate that by means of recently developed technics in the field of gastrointestinal investigation, the diagnosis of mobile cecum with intermittent volvulus can at times be established during the chronic preobstructive phase of the disease.

The term "mobile cecum" must be clearly defined, for in some respects it is discredited by the same stigma which now appertains to the words "visceroptosis" and "intestinal putrefaction." Strictly speaking, the mobile cecum is, according to Harvey,<sup>1</sup> no abnormality at all, and Berry<sup>2</sup> showed that the cecum in all but 6 per cent of persons is completely invested by peritoneum and carries no mesentery. Unmindful of this fact, surgeons in the first part of the twentieth century carried out numerous cecopexies in order to prevent kinking and twisting of the unattached cecum.<sup>3</sup> Their overenthusiasm caused the whole conception of the mobile cecum to fall into disrepute and obscured the fact that in some of the cases not only the cecum but also the ascending colon was endowed with mobility. Nonfixation of the ascending colon is a definite abnormality, which, if extensive enough, may predispose toward acute cecal volvulus or its chronic counterpart.

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1. Harvey, S. C.: Congenital Variations in the Peritoneal Relations of the Ascending Colon, Caecum, Appendix, and Terminal Ileum, *Ann. Surg.* **67**:641, 1918.

2. Berry, R. J.: The Caecal Folds and Fossae and the Topographical Anatomy of the Vermiform Appendix, Edinburgh, William F. Clay, 1897.

3. Wilms: Das Coecum mobile als Ursache mancher Fälle von sogenannter chronischer Appendicitis, *Deutsche med. Wchnschr.* **34**:1756, 1908. Waugh, G. E.: The Morbid Consequences of a Mobile Ascending Colon, with a Record of One Hundred and Eighty Operations, *Brit. J. Surg.* **7**:343, 1920. Houston, W. R.: The Mobile Right Colon, *J. A. M. A.* **93**:766 (Sept. 7) 1929.

A mobile right side of the colon represents an anomaly of fixation, a process which is considered to be the fourth and last stage in the embryologic development of the large bowel. After the first three stages—those of migration, rotation and descent—have taken place, the right side of the colon usually becomes fixed to the posterior parietal wall by obliteration of its mesentery. When some or all of this mesentery persists, a mobile cecocolon ensues, the degree of mobility being determined in part by the width and the extent of the mesenteric attachment. Since all degrees of this condition are possible, the demarcation between what constitutes the normal and what the abnormal is difficult to make. It is suggested that if the term "mobile cecum" is to have any clinical significance, its application be limited to a cecocolon which usually lies in its proper position but which potentially is subject to a process of rotation in the intact abdomen of the living person.

Little correlation can be demonstrated between vertical or horizontal (i. e., nonrotatory) mobility of the cecum and the incidence of clinical symptoms. Kantor and Schlechter,<sup>4</sup> in a series of 383 roentgen examinations, observed that in 10.4 per cent of their cases there was evidence of a cecum with a vertical range of movement of  $2\frac{1}{2}$  inches (6.35 cm.) or more, but they could not discover any association between this degree of mobility and the occurrence of headache, vomiting, pain in the lower part of the abdomen or constipation. Likewise, the demonstration in the cadaver that a cecum can be rotated and twisted has little clinical significance. In a series of 640 necropsies, Wandel<sup>5</sup> found that the cecum was mobile enough to allow "kinking, torsion and displacement" in 66 instances (10.3 per cent), and von Thun<sup>6</sup> felt that he could create volvulus of the cecum in 72 (21.3 per cent) of 338 cadavers; yet in each series, a history of symptoms which could be ascribed to the cecal anomaly was discovered only once. Many other authors have examined autopsy material to determine the frequency with which a mesentery persists on the right side of the colon, but usually without any attempt to employ uniform criteria or to establish any correlation with clinical symptoms. Table 1 lists some of the reported results.

From these figures it is obvious that slight mobility of the cecocolon is common. Far less frequent is the cecocolon sufficiently unattached to allow the occurrence of a spontaneous volvulus. In only 7 cases (1.1 per cent) in Wandel's<sup>5</sup> series did autopsy material show a mobility of the cecocolon as extensive as that present in 4 clinical cases of acute cecal volvulus. Other factors besides such a definite lack of fixation are, how-

4. Kantor, J. L., and Schlechter, S.: Colon Studies: VII. Variations in Fixation of the Ceco-Colon; Their Clinical Significance. *Am. J. Roentgenol.* **31**: 751, 1934.

5. Wandel, O.: Ueber Volvulus des Caecum und Colon ascendens, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **11**:39, 1903.

6. von Thun, cited by Jacobsen.<sup>11</sup>

ever, important in determining whether the mobile cecocolon will give rise to clinical symptoms or not. Volvulus will probably not occur unless some suitable fixed point is present about which the loose bowel can rotate. Further, volvulus may be prevented by adhesions, by intra-abdominal tension or by the position of the other viscera. The importance of these accessory factors is demonstrated by the relative infrequency with which acute cecal volvulus occurs. Sweet<sup>7</sup> found that in 520 cases of acute intestinal obstruction exclusive of external strangulated hernia, only 6 (1.15 per cent) were due to volvulus of the cecum. Other authors give somewhat higher figures (Pratt and Fallis,<sup>8</sup> 5 to 6 per cent; Leonard and Derow,<sup>9</sup> 3 per cent; Toprower,<sup>10</sup> 3.2 per cent; Jacobsen,<sup>11</sup> 15 per cent), but even if the highest of these figures is taken, it is clear that not every person with an unattached cecocolon suffers from clinical symptoms.

TABLE 1.—*Frequency with Which a Persisting Mesentery Is Demonstrated on the Right Side of the Colon in Autopsy Material*

Author	Number of Necropsies	Percentage of Cases in Which There Was a Persisting Mesentery
Harvey <sup>1</sup> .....	105 (Infants)	13
Dreyer: <i>Beitr. z. klin. Chir.</i> 75:113, 1911.....	105	67
Fallon: <i>Boston M. &amp; S. J.</i> 109:600, 1913.....	100	24
Treves, cited by Harvey <sup>1</sup> .....	100	26
Smith: <i>Anat. Rec.</i> 5:549, 1911.....	982 (Infants)	31

The frequency with which a mobile cecum gives rise to chronic symptoms is difficult to determine. A review of some of the case reports in the literature (table 2) indicates that about 47 per cent of the patients with acute cecal volvulus suffer from chronic symptoms before the acute attack occurs; but this figure is probably low, for a number of the reports neglected to mention any history previous to that of the acute episode.

In addition, some persons probably experience recurring and transitory volvulus of the cecocolon without ever suffering complete intestinal obstruction. Sweet<sup>7</sup> and Corner and Sargent<sup>12</sup> each reported a case

7. Sweet, R. H.: Volvulus of the Cecum, *New England J. Med.* **213**:287, 1935.

8. Pratt, J. P., and Fallis, L. S.: Volvulus of the Cecum and Ascending Colon, *J. A. M. A.* **89**:1225 (Oct. 8) 1927.

9. Leonard, E. D., and Derow, S.: Volvulus: A Study of Twenty-Two Cases, *New England J. Med.* **218**:388, 1938.

10. Toprower, G. S.: Zwei Fälle von Volvulus coeci, *Wien. klin. Wchnschr.* **46**:1417, 1932.

11. Jacobsen, H.: Volvulus du caecum, *Acta chir. Scandinav.* **56**:181, 1924.

12. Corner, E. M., and Sargent, P. W. G.: Volvulus of the Cecum, *Ann. Surg.* **41**:63, 1905.

in which operation was undertaken because the history strongly suggested chronically recurring cecal volvulus. In both instances, laparotomy demonstrated the rotated and twisted ascending colon. The following case report is that of another patient with chronically intermittent volvulus of the mobile cecum; it is of interest because the diagnosis was unequivocally established before operation.

## REPORT OF A CASE

*Personal History.*—C. P., a white single woman of 20, entered the surgical service of the Massachusetts Memorial Hospitals on Jan. 26, 1941. She complained of intermittent attacks of pain in the lower part of the abdomen which began six years previously and had gradually increased in severity, frequency and duration.

TABLE 2.—Frequency with Which Chronic Symptoms Precede an Acute Cecal Volvulus

Author	Total Cases of Cecal Volvulus	Number of Cases in Which There Were Chronic Symptoms
Jacobsen <sup>11</sup> .....	8	6
Weinstein: <i>Ann. Surg.</i> <b>107</b> : 248, 1938.....	2	1
Pratt and Fallis <sup>8</sup> (included cases with malposition of the colon).....	3	2
Farley and Konwaler: <i>Am. J. Surg.</i> <b>48</b> : 664, 1940.....	1	1
Wandel <sup>6</sup> (all but 5 of these cases were collected from the literature)..	46	17
Toprower <sup>10</sup> .....	2	1
Homans: <i>Arch. Surg.</i> <b>3</b> : 395 (Sept.) 1921.....	3	3
Grace: <i>Canad. M. A. J.</i> <b>38</b> : 346, 1938.....	2	1
Corner and Sargent <sup>12</sup> .....	5	1
McGowan: <i>Proc. Staff Meet., Mayo Clin.</i> <b>11</b> : 337, 1936.....	1	1
Sweet <sup>7</sup> .....	7	3
Bundschuh: <i>Beitr. z. klin. Chir.</i> <b>85</b> : 58, 1913.....	1	1
Total.....	81	39(47%)

At first, the symptoms had consisted of crampy sensations localized in the right lower quadrant of the abdomen; but subsequently the pains involved the left lower quadrant as well and were accompanied by moderate distention of the lower part of the abdomen. Immediately preceding admission, the patient had suffered two attacks which were complicated by nausea and vomiting. Precipitating factors appeared to be physical exercise or the ingestion of a heavy meal. Relief was obtained by lying down, by applying hot water bags or by massive enemas. Appendectomy had been performed five years before admission but had not relieved the symptoms.

The patient presented also two additional gastrointestinal complaints. One of these consisted of mild "indigestion" appearing five to fifteen minutes after eating and characterized by a heavy epigastric sensation. The other, marked constipation, was so severe that at one period in her life, bowel movements occurred only once every ten days. No history of cardiovascular, urinary or neuromuscular abnormalities was elicited. The menses were irregular and painful but apparently had no connection with her chief complaint.

*Familial History.*—Two cousins of the patient had died of bowel stoppage; one in youth, the other in middle adult life.

*Physical Examination.*—The patient was of average weight and height. Except for mild tenderness throughout the abdomen, no abnormalities were revealed.

*Laboratory Data.*—The urine contained no sugar, albumin or abnormal elements in the sediment. The hemoglobin content was 95; the erythrocyte count was 4,800,000; the leukocyte count was 7,300. The differential leukocyte count was normal. The stools were brown, formed and negative to the guaiac test.

*Roentgen Studies.*—A gastrointestinal series of roentgenograms revealed no abnormalities of the stomach or the duodenum. Plates taken five and twenty-four hours after the ingestion of the barium sulfate meal showed the opaque material in the ascending colon, which presented a normal outline. A roentgenogram taken after the patient had been given an enema of barium sulfate demonstrated flatus in the small bowel and what appeared to be a dilated intestinal loop, partially obscuring the ascending colon (*A* in figure). After the patient had evacuated the bowel, the same abnormalities were visible but to a lesser degree. A study of the small bowel, with roentgenograms taken every hour for seven hours after the patient had taken barium sulfate by mouth, showed no abnormalities; and the ascending colon, which contained opaque material in the last three films, appeared normal in outline, size and position. The roentgenologic department, while recognizing that the films taken after giving the enema of barium sulfate were suggestive, did not feel an adequate interpretation could be given, especially since similar changes in the bowel could not be demonstrated in either the gastrointestinal series or the study of the small bowel.

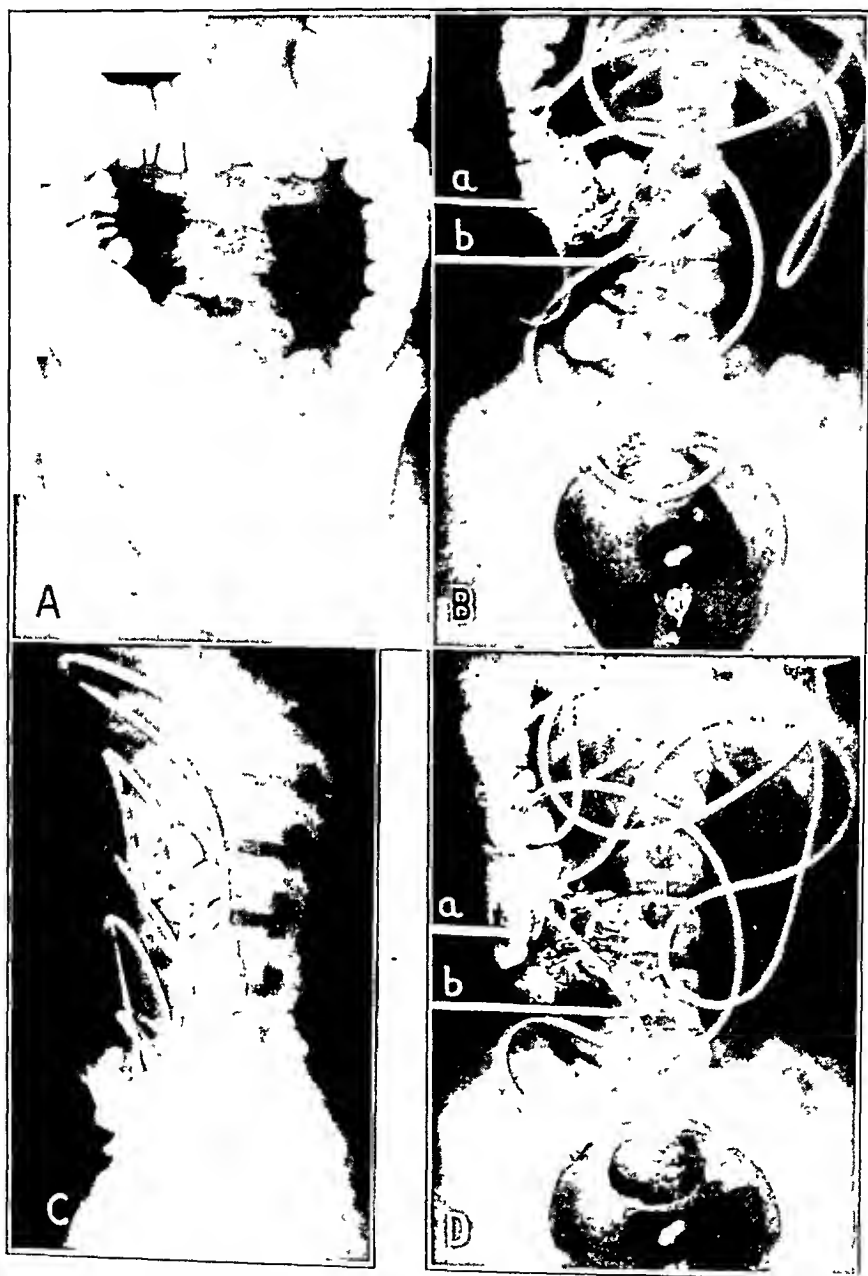
*Special Studies.*—Since gastrointestinal roentgenograms had suggested that some intestinal abnormality was present but had not clarified the nature of this disorder, further diagnostic study was indicated. Ingelfinger and Abbott<sup>13</sup> showed that by employing two modifications of the Miller-Abbott method of small intestinal intubation,<sup>14</sup> specific information can often be obtained in cases in which the usual examinations yield questionable results. The first of these modifications consists of recording the small intestinal muscular activity, a method which was first used by Abbott and his collaborators<sup>15</sup> in studying the small bowel when obstructed and when under the influence of drugs. In the present case, a perfectly normal record of small intestinal activity was obtained. An unusual feature was encountered, however, when the patient was subjected to fluoroscopic examination after the record had indicated that the tip of the tube had entered the cecum. Instead of appearing in the right lower quadrant of the abdomen, as was anticipated, the tip of the tube was seen to lie in front of the third lumbar vertebra.

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13. Ingelfinger, F. J., and Abbott, W. O.: Intubation Studies of the Human Small Intestine: XX. The Diagnostic Significance of Motor Disturbances, *Am. J. Digest. Dis.* 7:468, 1940.

14. Miller, T. G., and Abbott, W. O.: Intestinal Intubation: A Practical Technique, *Am. J. M. Sc.* 187:595, 1934.

15. Abbott, W. O., and Pendergrass, E. P.: Intubation Studies of the Human Small Intestine: V. The Motor Effects of Single Clinical Doses of Morphine Sulphate in Normal Subjects, *Am. J. Roentgenol.* 35:289, 1936. Abbott, W. O.; Zetzel, L., and Glenn, P. M.: Observations on the Motor Activity of the Obstructed Small Intestine Made During the Course of Treatment by Intubation, *Am. J. M. Sc.* 195:279, 1938.



In *A*, the colon has been outlined by an enema of barium sulfate. Flatus shadows appear in the small intestinal loops. In the right lower quadrant of the abdomen a large dilated loop of bowel is filled with the opaque medium. In *B*, barium sulfate outlines the cecocolon, which is displaced medially and sharply angulated at *a*. The tip of the tube lies in the cecum, just beyond the ileocecal valve. The distal portion of the tube (*b*) lies in the terminal part of the ileum, which enters the cecum from the wrong direction. *C*, a lateral view showing the angulation in the ascending colon. In *D*, the cecocolon is now in its usual position, but the angulation at *a* is more acute. The terminal part of the ileum (*b*) now enters the cecum in the usual manner.

At this point, the second modification of the Miller-Abbott procedure, a modification originally described by Abbott and Johnston,<sup>16</sup> was employed. A thin suspension of barium sulfate was injected through the tube in order to delineate that part of the intestine which contained the tip. By means of the fluoroscope, the injected opaque substance was seen to flow in two directions, orad and caudad, but it did not regurgitate backward along the tube. A roentgenogram taken at the same time (*B* in figure) showed that the terminal part of the ileum was entering the cecum from the wrong direction (i. e., from right to left) and that the cecocolon was both displaced and sharply angulated. The angulation is more noticeable in *C* in the figure. After the patient's position on the fluoroscopic table was changed, the ileum and the cecocolon started to move without any further manipulation by the operator and assumed the position shown in *D* in the figure. The ileum was now entering the cecum in the usual manner (i. e., from left to right), and the cecocolon lay in its normal position, although the angulation in the ascending colon was more acute. These roentgenograms offer definite proof that the cecocolon in this patient rotated through an arc of 180 degrees under the ordinary stimuli of bodily movement and gravity.

At operation, the cecocolon was found to be freely movable, and both the ascending and the descending colon possessed long mesenteric attachments. In an attempt to prevent any further episodes of volvulus, the cecocolon was fixed to the right posterior parietal wall. At the time of writing, the patient has not suffered any further attacks of pain in the lower part of the abdomen, distention, nausea and vomiting since operation. Her complaint of "indigestion" has so far persisted, but the constipation is much less marked and easily controlled with liquid petrolatum.

#### COMMENT

This case offers definite demonstration of two phenomena which heretofore have been supported only by inference based on observations made at the operating or the autopsy table. In the first place, the studies carried out with the aid of the Miller-Abbott tube demonstrate that when the proper anatomic conditions obtain, the cecocolon can rotate through an angle of 180 degrees in the intact abdomen of a living person and that the stimulus for this rotation need be no more than a simple bodily movement. It is claimed that a torsion of more than 180 degrees is necessary to produce the signs and symptoms of volvulus. With regard to the present case, this contention is probably correct, for when the cecocolon had undergone the twist of 180 degrees (*B* in figure), the patient experienced no symptoms, and a roentgenogram showed no evidence of intestinal obstruction.

In the second place, this case demonstrates that a cecocolon of enough mobility to rotate through an arc of more than 180 degrees can at times be subject to further torsion; when this happens, typical, but usually transitory, cecal volvulus is produced. In the figure, *B* shows the unmistakable characteristics of intestinal obstruction: a dilated intestinal loop and the accumulation of flatus in the small bowel. Hence, there

16. Abbott, W. O., and Johnston, C. G.: Intubation Studies of the Human Small Intestine: X. A Non-Surgical Method of Treating, Localizing and Diagnosing the Nature of Obstructive Lesions, Surg., Gynec. & Obst. 66:691, 1938.

can be little doubt that the abdominal pain and distention in this case were occasioned by intermittent and partial volvulus of the mobile cecocolon.

As stated previously, a mobile cecocolon with intermittent volvulus is a rare condition. Nevertheless, it is important to make the diagnosis whenever possible, for surgical fixation of the ascending colon will usually alleviate the symptoms of intermittent intestinal obstruction. Even more important, fixation should prevent the occurrence of a cecal volvulus which fails to reduce itself and which must be treated as an acute and dangerous surgical emergency.

As is true in the present case, the history of patients with chronic cecal volvulus is characteristic. Usually the person is young and active. The symptoms are those of intermittent intestinal obstruction: crampy pains most frequently involving the lower part of the abdomen, distention and, occasionally, nausea and vomiting. These symptoms are usually precipitated by the ingestion of a heavy meal or by physical exercise, persist anywhere from one-half to four hours and then usually subside spontaneously. Almost invariably, the patient has severe constipation, and frequently a fruitless appendectomy has been performed.

If a patient with such a history is encountered and if the usual clinical and roentgen studies are negative or inconclusive, special studies similar to those used in the present case are indicated. It is not maintained that in every case mobile cecocolon with a tendency toward intermittent volvulus can be diagnosed, but if the Miller-Abbott method of intestinal intubation and its modifications are used as diagnostic procedures, the chances of recognizing such an obscure condition as a mobile cecocolon are enhanced.

#### SUMMARY

If the term mobile cecum is to have any clinical significance, its application should be limited to a cecocolon which usually lies in its proper position but which potentially is subject to a process of rotation in the intact abdomen of the living person.

Mobile cecocolon with a tendency toward intermittent volvulus is a rare condition. About one half of the patients who come to operation because of acute cecal volvulus suffer from chronic symptoms previous to the acute attack.

Roentgenograms of a patient whose case is presented demonstrate that in the intact abdomen of this living person: (1) the cecocolon could easily rotate through an angle of 180 degrees and (2) transient intestinal obstruction due to cecal volvulus could occur.

By using two modifications of the Miller-Abbott method of small intestinal intubation, the possibilities of diagnosing mobile cecocolon are increased.

Dr. Lois Miller of the roentgenologic department and Dr. Hollis Albright of the surgical department helped in the diagnosis and in the treatment of this patient.



# LIPOSARCOMA

## REPORT OF NINE CASES

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A survey of the literature indicates that liposarcoma is a neoplasm of extremely rare occurrence. Virchow<sup>1</sup> (1857) is credited with the first accurate histologic study of this tumor, and in 1939, Lingley<sup>2</sup> reported a case of liposarcoma which was noted as the seventy-second one to be recorded.

Recently, however, there has arisen the impression that these figures do not represent a true estimate of the clinical frequency of liposarcoma. The extremely variable microscopic features shown by liposarcoma (stressed by Geschickter<sup>3</sup> and others) may have occasioned the classification of certain of these tumors as endothelial, carcinomatous or xanthomatous neoplasms. At times, liposarcoma has undoubtedly been mistakenly diagnosed as fibrosarcoma.

From Jan. 1, 1931, to Jan. 1, 1941, approximately 16,000 patients with tumor were admitted to the Veterans Administration Facility, and from this group a diagnosis of liposarcoma was made in 9 instances. This seems to suggest a somewhat higher frequency than is indicated by the paucity of reports in the literature.

## REPORT OF CASES

CASE 1.—Q. E. K., a white barber aged 68, was admitted to the hospital on April 11, 1939. The familial history was negative. The illness presented dated from Jan. 1, 1939; at that time the patient noted a lump under the skin just below the right scapula. It was small, hard and freely movable. It grew rapidly, reaching

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From the Tumor Service and the Pathological Laboratory of the Veterans Administration Facility.

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1. Virchow, cited by Geschickter.<sup>3</sup>

2. Lingley, J. R.: Liposarcoma: Case Report, *Am. J. Roentgenol.* **41**:851-854 (May) 1939.

3. Geschickter, C. F.: Lipoid Tumors, *Am. J. Cancer* **21**:617-641 (July) 1934.

a diameter of 6 inches (15.2 cm.) in a few weeks, and protruded about 4 inches (10.2 cm.) above the surface. The family physician incised the tumor but did not attempt removal.

The site of the incision broke down, and the tumor assumed a cauliflower-like growth. From the time the tumor was noted until admission, the patient lost 30 pounds (13.6 Kg.).

On admission the tumor was 8 inches (20.3 cm.) in diameter, not painful and firmly attached to the underlying tissues; the surface was fungating. There was no demonstrable adenopathy. Roentgen examination of the chest revealed nothing of interest. Kahn and Wassermann tests were negative. Urinalysis was negative.

Wide excision of the growth was done with a Bovie knife and included part of the underlying fascia and the latissimus dorsi muscle. Punch grafts were applied to the surface of the wound. There was complete healing at the time of discharge, July 7, and the patient appeared to be well. He had gained 4 pounds (1.8 Kg.).

On November 1 the patient was readmitted with a small lump 1 cm. in diameter in the scar. This was excised and found to be a keloid.

Examination on Aug. 15, 1940 showed the patient free from evidence of metastasis or recurrence. He is well at the time of writing.

*Gross Description.*—The tumor measured 10 by 8 by 8 cm. The surrounding skin and soft tissues were attached. The surface was red with a cauliflower appearance. The cut section was firm and glistening and yellowish white. The tumor was not encapsulated. It had not invaded the surrounding soft tissues.

*Microscopic Description.*—The cells were oval and polyhedral in shape and showed great variation in size. In some, the cytoplasm was vacuolated. The vacuoles stained with sudan III and were doubly refractive. The nuclei were eccentrically placed and for the most part were hyperchromatic. There was some variation in the chromatin content of the nuclei, and they varied markedly in size and shape. Mitoses were frequent. The diagnosis was liposarcoma.

CASE 2.—H. S., a white bank clerk aged 44, was admitted to the hospital on Feb. 2, 1938. The past history revealed the usual diseases of childhood. Venereal diseases were denied.

The illness dated from the patient's discovery of a mass in the upper part of the abdomen three months earlier. The tumor was not painful. Since the discovery of the tumor, the patient suffered frequent spells of dizziness and had fainted on a number of occasions; he had lost 14 pounds (6.4 Kg.).

Examination revealed a large mass in the right upper quadrant of the abdomen, extending to the left of the midline and downward to the level of the crest of the ilium. The tumor presented no definite outline and was not tender; it moved with respiration.

Pyclograms showed no dye in the right kidney. Preoperative irradiation was given with no response. Roentgen examination of the gastrointestinal tract, the gallbladder and the skull revealed no abnormalities.

Operation on March 17 revealed a large retroperitoneal tumor. This mass involved the blood supply to the right kidney but did not invade the kidney. The kidney was removed. The postoperative recovery was good. The patient gained

12 pounds (5.4 Kg.) and was discharged on June 2 with no demonstrable evidence of metastasis or recurrence. Extensive postoperative irradiation was given.

The patient went back to work and continued to gain weight.

At the end of a year the abdomen began to enlarge; ascites developed, and edema of the lower extremities was noted. The patient lost weight, and the course was steadily downhill, until death occurred on July 25, 1940.

*Gross Description.*—The resected tumor weighed 5,000 Gm. It was grayish white, firm, friable and vascular. The mass was not well encapsulated but was completely removed.

*Microscopic Description.*—The cells were round, polyhedral and spindle shaped. They were vacuolated. The nuclei were hyperchromatic for the most part, but the chromatin content varied in amount. Many mitoses were noted. The stroma was scanty. The growth was well vascularized. The diagnosis was liposarcoma.

*Autopsy.*—Autopsy revealed a massive lesion; the entire right lobe of the liver was replaced by tumor, the center of which had broken down. There was an extensive retroperitoneal tumor mass which was of identical histologic structure as the original tumor. The structure of the tumor of the liver also was identical.

CASE 3.—E. O. C., a white laborer aged 52, was admitted to the hospital on Dec. 13, 1938. The familial and personal histories revealed nothing of interest. The illness dated from 1930, when three masses were excised from the patient's left hip. The growth recurred in 1932 and was excised; a later recurrence was excised in 1934. No operation records or pathologist's report were available.

At the time of admission to the hospital, the patient complained of tumor masses in the left buttock; these had begun to grow about a year previously.

Examination revealed a well developed, rather obese man in good general physical condition. Three tumor masses were noted in the left buttock, firmly adherent to surrounding soft tissue and old excision scars. Roentgen examination of the chest and the skeleton found no evidence of metastasis.

Three masses were widely excised with a Bovie knife on Jan. 27, 1939. The three masses were 7 to 10 cm. in diameter and adherent to scars and surrounding soft structures. The masses were partially encapsulated, but in places they apparently invaded the muscle.

*Gross Description.*—The tumor tissue was firm in consistency and was friable. Grossly, the tumor did not appear to be fat.

*Microscopic Description.*—Many large, mature fat cells were seen, along with many groups of immature large light-staining cells with firmly granular cytoplasm. The nuclei were round, hyperchromatic and eccentrically placed. Many of the cells had two or three nuclei. No mitoses were present. The diagnosis was liposarcoma.

The patient was discharged in good condition on February 24. At the time of writing, there is no evidence of recurrence.

CASE 4.—J. C. S., a white man aged 38, was admitted to the hospital on Dec. 27, 1934. His father had died of cancer; otherwise, the familial history revealed nothing of note. The personal history was not important.

Fifteen years previously, the patient had noted a small freely movable lump on the right lateral wall of the chest, just below the axilla. Two years before admission, the lump began to grow; it was excised six months before admission.

The patient stated that the excised tumor weighed 3 pounds (1.3 Kg.) and was diagnosed as Hodgkin's disease. The slide of this tumor was reviewed at the time of admission, and a diagnosis of liposarcoma was made.

Large discrete masses were noted in the right axillary and cervical regions. The original tumor and these axillary and cervical masses were subjected to intensive irradiation, with no effect on the size. A sinus developed in the axillary region and drained profusely. Surgical excision of this sinus was done, and death resulted from massive postoperative hemorrhage from the operative wound. There was no autopsy.



Fig. 1. (case 4).—Photograph showing massive fungating ulcerative tumor of the wall of the chest prior to surgical excision.

CASE 5.—H. D. B., a white farmer aged 49, was admitted to the hospital on April 4, 1940, from Veterans Administration Facility, Fayetteville, Ark., with a diagnosis of sarcoma of the right thigh. The patient stated that he had watched the tumor grow from the size of a bean to that of a watermelon during the past eight years. At first, he was able to pick up the nodule and roll it under the skin. In four years it grew to the size of a walnut. In September 1934, it was a little larger than a hen's egg. The growth was steady but slow, until the last eighteen months before admission, during which it grew rapidly to massive proportions.

An attempt had been made by the family physician to remove the growth, but he had encountered excessive bleeding and closed the wound. On admission to this hospital, the patient was in fairly good general physical condition; he was well nourished and had lost little weight. He was confined to bed because of the

ility occasioned by the tumor occupying the entire anteromedial aspect of right thigh. The mass extended from the knee to the inguinal ligament and with the ligament retroperitoneally, occupying the entire right lower quadrant of abdomen. This was interpreted as extension of the tumor to the abdominal retroperitoneal regions.

Although only a few rales were heard at the base of the right lung, roentgenosis showed a 4 cm. spherical shadow in the right cardiophrenic angle; this was considered indicative of metastasis. Roentgenograms of the thigh showed no involvement of the femur.



Fig. 2 (case 5).—Photograph showing involvement of the entire anteromedial aspect of the right thigh.

The tumor was considered inoperable. Biopsy was done.

*Biopsy.*—The section showed numerous irregular cells, most of which tended to be spindle shaped. The nuclei were hyperchromatic, round or slightly elongated and eccentrically placed. The cytoplasm was granular and vacuolated. Occasional mitoses were seen. A few giant cells were noted.

At his request, the patient was allowed to return home.

**CASE 6.**—W. D. S., a white man aged 45, a farmer and barber by profession, entered the hospital on March 27, 1940. The familial and personal histories revealed nothing of interest. Illness had been noted three months before admission

with the onset of pain in the upper part of the abdomen and vomiting after meals. During this time, the patient lost 40 pounds (18.1 Kg.).

Examination revealed an emaciated man with the appearance of chronic illness. A large hard tumor was palpated in the epigastrium and the upper left quadrant of the abdomen. The liver and the spleen were not palpable.

Rectal examination revealed nothing of note. It was impossible to make a gastrointestinal roentgen series owing to incessant vomiting. A diagnosis of probable tumor of the stomach was made, and exploratory laparotomy was done.

The operation revealed a large orange-colored nodular tumor measuring 8 by 15 cm and located in the upper two thirds of the mesentery of the jejunum.

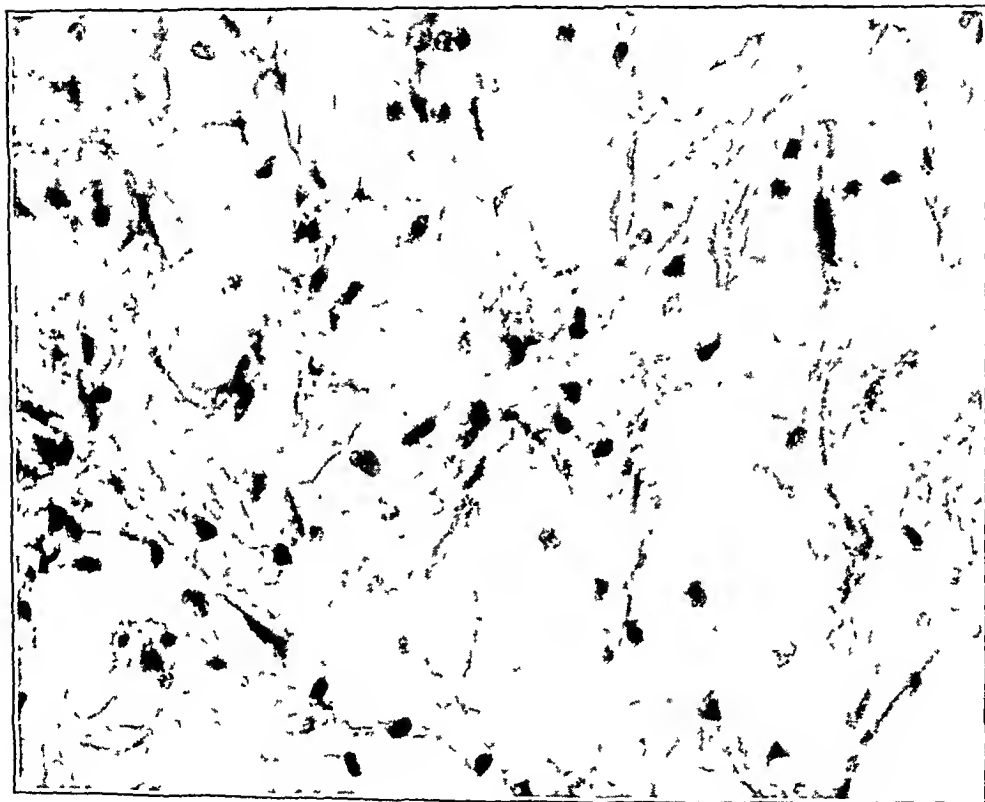


Fig 3 (case 3).—Photomicrograph ( $\times 286$ ) showing growth consisting of large mature fat cells with eccentrically placed nuclei. Small irregular foamy cells are also present.

Material for biopsy was taken, and the abdomen was closed, the tumor being judged inoperable. The tissue removed was firm in consistency and yellowish white in color.

*Biopsy.*—Mature fat cells and aggregations of large and small granular cells were seen. These cells had small hyperchromatic nuclei. Numerous vacuoles were seen which took the fat stain. Occasional mitoses were seen. The diagnosis was liposarcoma.

The patient was given postoperative irradiation with no evident diminution in the size of the tumor.

At the time of writing, the patient is ambulant, but the tumor shows constant increase in size, and the outlook is hopeless.

CASE 7.—J. P., a white man aged 39, was admitted to the hospital on April 7, 1939. The familial and personal histories revealed nothing of note.

About one year previously, the patient had noted that the abdomen was enlarging. He also noted a loss of weight and strength. He consulted the family physician who advised him that he had an abdominal tumor and advised an operation. This was done, and the physician reported the presence of a retroperitoneal tumor the size of a football, which he considered inoperable. Biopsy was done and the diagnosis of fibrosarcoma made. The tumor was yellowish and nodular. The regional lymph nodes were invaded. After recovery from this operation, the patient was transferred to this hospital for further treatment. Another exploratory operation

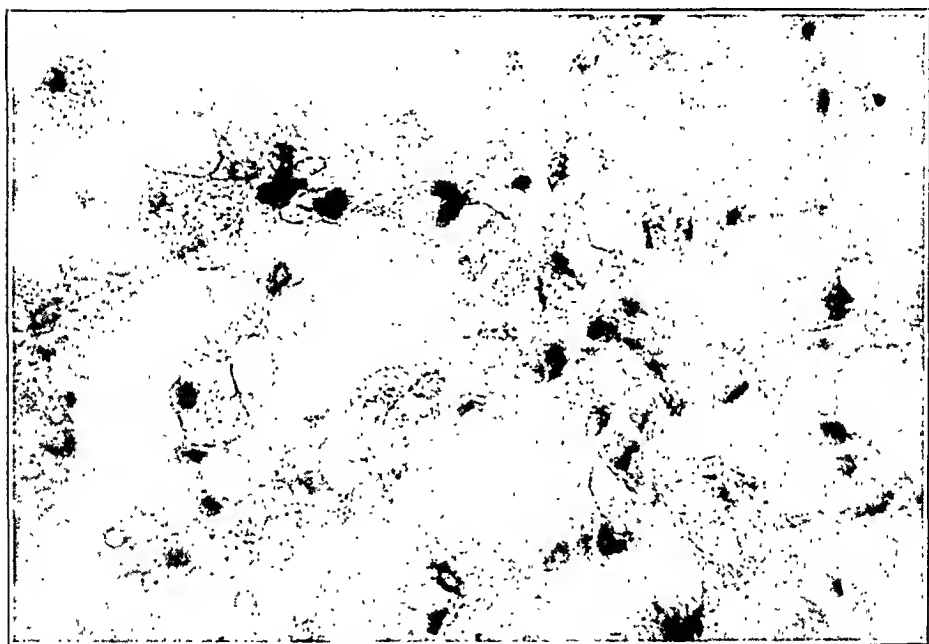


Fig. 4 (case 1).—Photomicrograph of high power magnification showing large cells containing fat. The section was stained with sudan III.

was done, and a retroperitoneal tumor, weighing 15 pounds (6.8 Kg.), was removed. The mass was horseshoe shaped, lying on each side of the spine and attached at the midline at the level of the duodenum. Small remnants of the tumor and large infiltrated lymph nodes could not be removed.

The patient recovered rapidly and gained weight. He was discharged June 19. Roentgen examination showed no evidence of metastasis. The patient is well at the time of writing.

*Gross Description.*—The tumor weighed 15 pounds (6.8 Kg.). It was nodular, firm and grayish white. It had a firm capsule.

*Microscopic Description.*—Histologic examination revealed large mature fat cells and masses of polygonal and spindle-shaped cells with granular cytoplasm containing vacuoles. Some of these cells had vesicular nuclei, and others had small hyperchromatic nuclei. A few mitoses were seen. A small number of

lymphocytes, eosinophils and foreign body giant cells were noted. The diagnosis was liposarcoma of a low degree of malignancy.

CASE 8.—A. M. R., a white farmer aged 45, was admitted to the hospital on April 10, 1936. The familial and personal histories revealed nothing of interest.

About fifteen years previously, the patient had noted a small lump in the right thigh. About eighteen months prior to admission, the lump began to grow rapidly. At the Veterans Administration Facility, Indianapolis, the tumor was removed from the upper part of the right popliteal space. It was 3 inches (7.6 cm.) in diameter, grayish white and homogeneous. It was encapsulated.

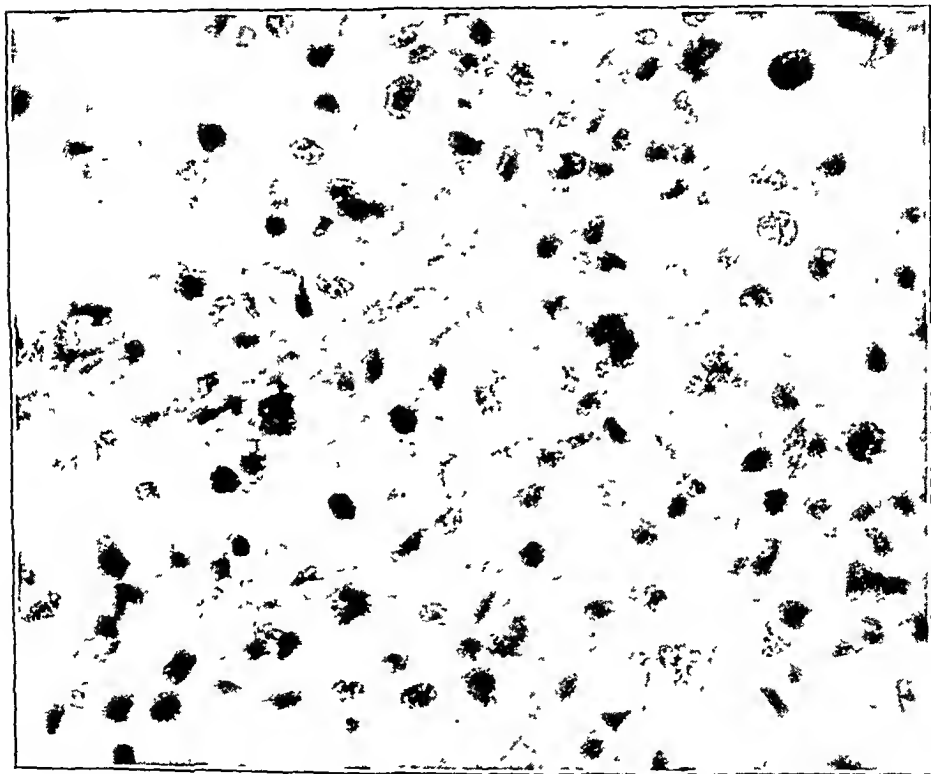


Fig. 5 (case 8).—Photomicrograph ( $\times 286$ ) showing moderately cellular tumor. The cytoplasm is granular and vacuolated; the nuclei are dark and eccentrically situated.

*Microscopic Examination.*—Histologic examination revealed a moderately cellular growth made up of spindle-shaped and oval-shaped cells. In the oval cells, the nuclei were small and hyperchromatic, often eccentrically placed. Both types of cells were granular and vacuolated. The vacuoles in some instances pushed the nuclei to one side. An occasional mitosis was noted. The diagnosis was liposarcoma of a low degree of malignancy.

This patient received no irradiation. Roentgen examination of the chest and the bones showed no evidence of metastasis.

The patient is well with no evidence of recurrence at the time of writing.

CASE 9.—J. L. W., a white salesman aged 45, was admitted to the hospital on July 20, 1936. The familial and personal histories presented nothing of note. Two



months prior to admission, the patient noted a nodule in the left hip. It grew progressively larger.

Shortly after the patient was admitted, the tumor was resected from the left gluteal region.

*Gross Description.*—The resected tumor was 15 cm. in diameter; it was grayish yellow and white, with small areas of hemorrhage and necrosis. It had a thin capsule. The surface was glistening and mucoid. There was evidence of invasion of the soft tissues.

*Microscopic Examination.*—Histologic examination revealed cells of irregular size and shape—spindle shaped, round and polygonal. Occasional cells were

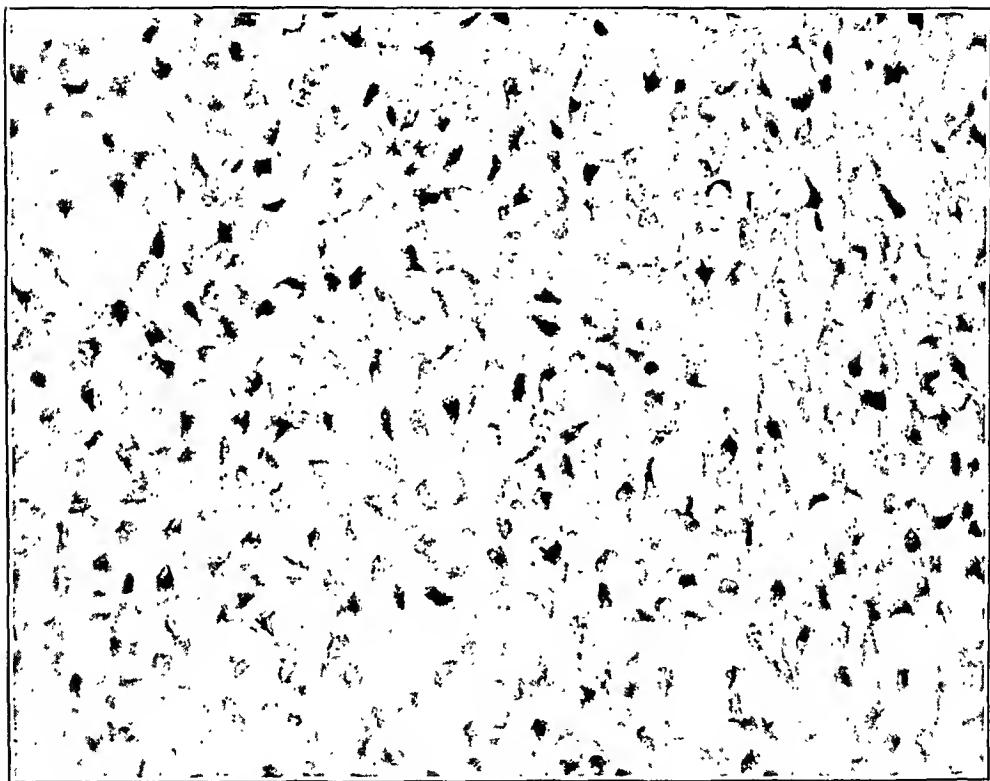


Fig. 6 (case 9).—Photomicrograph ( $\times 286$ ) showing vacuolated cells and dark nuclei; the latter are eccentrically placed and vary in size and shape.

recognized as adult fat cells. The majority of the cells were granular with reticular nuclei. Many cells contained vacuoles which had pushed the nuclei aside. The smaller cells had eccentrically placed small hyperchromatic nuclei and also showed vacuoles. An occasional mitotic figure was seen. There were extensive areas of myxomatous degeneration. The diagnosis was liposarcoma of a low degree of malignancy.

Roentgen examination of the chest and the bones showed no evidence of metastasis.

Intensive postoperative irradiation was given. The patient is well with no evidence of recurrence at the time of writing.

## COMMENT

*Location.*—The most frequent site of origin for liposarcoma seems to be in the soft tissues of the lower extremity; the second most frequent, the retroperitoneal space. In a series of 12 cases of liposarcoma reported by Geschickter, in 5, the tumor was on the thigh or the leg; in 3, in the breast; in 2, in the forearm and the arm; in 1, on the back, and in 1, in the thorax. In a series of 51 cases collected by Robertson,<sup>4</sup> in 42 per cent it was in the thigh or the lower part of the limb.

Various other sites of origin include the mediastinum,<sup>5</sup> the vulva<sup>6</sup> and bone.<sup>7</sup>

The following sites of origin were noted in the cases described in this report: the gluteal region and the thigh in 4 cases; the retroperitoneal region in 3 cases; the right lateral wall of the chest just below the axilla in 1 case; the right scapular region in 1 case.

*Clinical Course and Prognosis.*—The clinical history of liposarcoma almost invariably includes the discovery by the patient or the physician of a mass or lump. The tumor may grow slowly over a period of years, or the rate of growth may be extremely rapid. One patient in our series (case 5) observed a tumor of the right thigh grow from the size of a bean to that of a watermelon over a period of eight years. Another patient (case 1) observed an increase in a small tumor of the scapular region to a diameter of 6 inches (15.2 cm.) with a protrusion of 4 inches (10.2 cm.) above the skin surface in six weeks. In case 8, the tumor was known to be present fifteen years before it exhibited growth.

When the tumor is retroperitoneal, the usual signs and symptoms of neoplasms of this region are encountered: enlargement of the abdomen and derangement of functions in the various abdominal and pelvic organs caused by compression and encroachment of the expanding mass.

When the tumor exhibits signs of rapid growth and activity, the usual clinical signs of malignancy ensue.

Recurrence and metastasis are the rule with liposarcoma. These may be encountered early or late. Lingley noted in this regard:

All authors are agreed on the marked degree of malignancy of this tumor. The mass is usually encapsulated and, if simply shelled out or excised, it invariably

4. Robertson, H. E.: *Lipoma Myxomatodes*, J. M. Research **35**:131-146, 1916.

5. Perkins, C. W., and Bowers, R. F.: *Liposarcoma of Mediastinum and Lung*, Am. J. Roentgenol. **42**:341-344 (Sept.) 1939.

6. Taussig, F. J.: *Liposarcoma of the Vulva*, Am. J. Obst. & Gynec. **33**:1017-1026 (June) 1937.

7. Stewart, F. W.: *Primary Liposarcoma of Bone*, Am. J. Path. **7**:87-93 (March) 1931.

recurs locally. Even fairly wide excision may be followed by local recurrence and metastasis. In Geschickter's series of 12 cases the tumor recurred after excision in every case but one which was only recently observed. No case was reported cured.

Geschickter found that the duration of symptoms from the first complaint until metastasis was known to occur averaged ten years in his series.

In the case reported by Taussig, a lump located in the left labium majus pudendi grew large in six months. It was enucleated, and the diagnosis of liposarcoma was made. It recurred in two weeks and at the end of six weeks it was 4 by 2.5 cm. in size. One-sided vulvectomy was done. Two months later widespread metastasis was evident in the lungs and the bones. Death ensued after six months.

Fender<sup>8</sup> reported a case in which a five year period elapsed after extirpation of a liposarcoma of the leg. At this time an intracranial metastasis was removed by operation, and at the time of this report the patient showed evidence of recurrence of the intracranial tumor.

Fender noted that "the few cases available for study seem to indicate that these tumors grow slowly, are radiosensitive, metastasize late and show a tendency to metastasize to the cranium." Dr. F. B. Mallory reviewed the sections of the original tumor of the leg in Fender's case and pronounced this tumor to be identical with the cranial tumor, concurring in the diagnosis of late intracranial metastasis from a primary liposarcoma of the leg.

In our series of 9 cases of liposarcoma, the outcome at the time of writing is as follows:

Case 1.—Patient is well with no signs of metastasis or recurrence after twenty months.

Case 2.—Recurrence occurred after one year; death, two months later.

Case 3.—There is no evidence of metastasis or recurrence after two years.

Case 4.—Recurrence occurred after six months; death followed massive hemorrhage subsequent to removal of recurrence by operation.

Case 5.—An enormous tumor of the right thigh, inoperable when seen at this hospital, is present; there is roentgen evidence of metastatic growth under the right cardiophrenic angle.

Case 6.—The retroperitoneal tumor, inoperable at exploratory operation, is growing; the outlook is hopeless.

Case 7.—Good postoperative recovery followed removal of the retroperitoneal tumor. Small remnants of the tumor and the infiltrated lymph nodes could not be removed. The patient is well after twenty months.

Case 8.—The patient is well with no evidence of metastasis or recurrence five years after removal of the tumor from the right popliteal space.

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8. Fender, F. A.: Liposarcoma: Case with Intracranial Metastases, *Am. J. Path.* 9:909-914 (Nov.) 1933.

Case 9.—The patient is well with no evidence of metastasis or recurrence four years and nine months after removal of the tumor from the left gluteal region.

Liposarcoma has been listed by certain authors as a radiosensitive tumor. In certain of our cases, irradiation was used with no demonstrable favorable effect.

*Diagnosis.*—The diagnosis of liposarcoma is naturally made by histologic examination. In case 4 of our series, the original tumor examined elsewhere was misdiagnosed as Hodgkin's disease. A review of the slides and a study of the recurrence showed liposarcoma.

Castleman, in discussing Lingley's report, said regarding the histologic diagnosis of liposarcoma:

. . . Throughout the tumor all shapes of fat cells from small embryonic fat cells to large adult fat cells could be found, a fact that definitely rules out fatty degeneration of fibrosarcoma, a condition that is sometimes erroneously called liposarcoma histologically.

*Pathologic Description.*—It is frequently noted that liposarcoma tends to be well encapsulated and may shell out easily at operation. Despite this fact, it often recurs locally and metastasizes. Recurrence and metastasis, however, frequently follow wide excision.

Fender described the histologic picture in his case of liposarcoma as follows: "None of the cells were differentiated into adult fat cells, but they had granular cytoplasm, eccentric nuclei and alveolar arrangement which are considered characteristic."

Perkins and Bowers' well encapsulated specimen of liposarcoma was microscopically extremely cellular. They described it histologically as follows:

. . . [The] basic architecture might be said to resemble that found in liver, in that there were small lobules with a central vessel about which the neoplastic elements were growing. Each of these in turn presented a thin capsule-like structure of cellular fibrous tissue, areas of which presented hyaline degeneration.

. . . The cells were small, loosely arranged, with but little cytoplasm. Many of the nuclei were hyperchromatic, and were of the wheel-like type, resembling those of plasma cells. Others, however, had more than a mere rim of cytoplasm; their nuclei were larger but did not stain deeply and suggested an endothelial origin. In attempting further to identify their origin, a section stained with sudan III showed that they almost invariably contained tiny fat granules. Because of their primitive appearance, and the large amount of fat, this tumor was considered lipogenic. Diagnosis was liposarcoma. . . .

In the case reported by Taussig, sections of the tumor were sent to Dr. James Ewing for study and confirmation of the diagnosis. His microscopic description of this liposarcoma was as follows:

Sections of the tumor stained with hematoxylin and eosin show a moderately rich cellular neoplasm separated into smaller and larger masses of fine and coarse bands of fibrous tissue. The tumor cells are oval to spindle in shape and vary mark-

edly in size; the nucleus is small, and the cytoplasmic structure contains fat globules of varying size and number. The cytoplasm is finely granular. These cells represent varying stages in the development of fat cells. The reticulum of the tumor demonstrated by the Foot modification of the Bielschowsky silver impregnation method is abundant in quantity and mainly in the form of a plexus surrounding each cell, the whole forming a network. The intracellular fat was demonstrable in the frozen section, stained with sudan III. The lymph nodes present a moderate hyperplasia, with no evidence of tumor cells.

Geschickter summarized the histologic picture of liposarcoma thus:

Liposarcoma shows extremely variable microscopic features. The predominating malignant tissue either resembles a fascial sarcoma with compact spindle cells or shows numerous immense tumor giant cells with degenerating nuclei and a large amount of foamy cytoplasm. Surrounding these malignant areas are islands of embryonic fat, adult fat, and myxomatous-like stroma. A small cell resembling a plasma cell or fetal cartilage cell is often seen. Whether it is a forerunner of the larger foam cell is not certain.

In our series of 9 cases of liposarcoma, the neoplasms were moderately cellular. The cells for the most part were round to spindle shaped and showed marked variation in size. The nuclei, as a rule, were small, frequently hyperchromatic and often eccentrically placed. The cytoplasm was finely granular and showed vacuoles of varying sizes. In some instances the vacuoles appeared to have displaced the nucleus toward the edge of the cell. As a rule, mitoses were few; mitotic figures were more abundant in the highly anaplastic metastasizing tumors. The stroma consisted of well vascularized fibrous connective tissue dividing the growth into cell aggregations of various sizes. The appearance of many of the smaller cells suggested embryonic fat. The presence of fat in the cells was demonstrated by sudan III or sudan IV stain.

#### SUMMARY

Nine cases of liposarcoma are described. These were encountered in the examination and treatment of 16,000 patients with tumor.

It is suggested that the clinical frequency of liposarcoma may be greater than the few cases reported in the literature would indicate.

# INTERVAL INTRACRANIAL HEMORRHAGE: ITS DIAGNOSIS AND MANAGEMENT

## ANALYSIS OF TWENTY-FIVE CASES

EMIL SELETZ, M.D.

LOS ANGELES

Since the vast majority of head injuries are of necessity treated by the industrial surgeon, this paper dealing with the diagnosis and the management of the only real surgical emergency among head injuries—the interval or delayed intracranial hemorrhage—should be of interest to him.

Interval hemorrhage is delayed intracranial bleeding that develops in either the extradural or the subdural space after an injury to the head. The injury may be slight; usually it is of sufficient severity to produce momentary unconsciousness. I have seen 4 professional boxers with interval hemorrhage after they had received a knockout blow in the ring. Twenty-two of the patients in this series of 25 suffered only a minor injury. Eleven had no period of unconsciousness.

The typical interval hemorrhage involves the middle meningeal artery. The sequence of events in this type of bleeding is as follows: The patient receiving a blow to the head, usually after a momentary period of unconsciousness, gets up and goes about his usual duties. During the injury, the middle meningeal artery has been torn. Within one or two hours, the patient complains of headache and often will place his hand over the region of the developing hemorrhage. Because of its location outside the dura, the bleeding artery produces an accumulation of blood between the dura and the cranial vault, and this stripping away of the dura from its attachment to the vault produces the pain. As the dura is being separated from the inner surface of the skull, other small branches of the meningeal artery are torn, and in this way the hemorrhage grows in size. This process within a few hours results in the accumulation of considerable tumor of blood, with resultant increase in intracranial pressure as well as pressure on the motor cortex of the brain. This relatively sudden increase in intracranial pressure produces gradually increasing drowsiness, stupor and, finally, coma, with slowing of the pulse and the respirations and contralateral motor weakness and perhaps paralysis. Frequently these

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symptoms are ushered in by a convulsion. Because of the anatomic location of the hemorrhage, pressure is exerted first in the face, then the arm area of the motor cortex; the convulsion begins in the face and the arm, and the paralysis develops in the same sequence, finally involving the lower extremity.<sup>1</sup>

During the development of the acute intracranial pressure there is a rise in the systolic blood pressure, while the diastolic remains relatively unchanged; this gives rise to a high pulse pressure with a characteristic full volume pulse. I have often seen blood pressures of 150 systolic and 60 diastolic or 180 systolic and 60 diastolic, giving a pulse pressure of 90 to 100. Spinal fluid findings show elevated

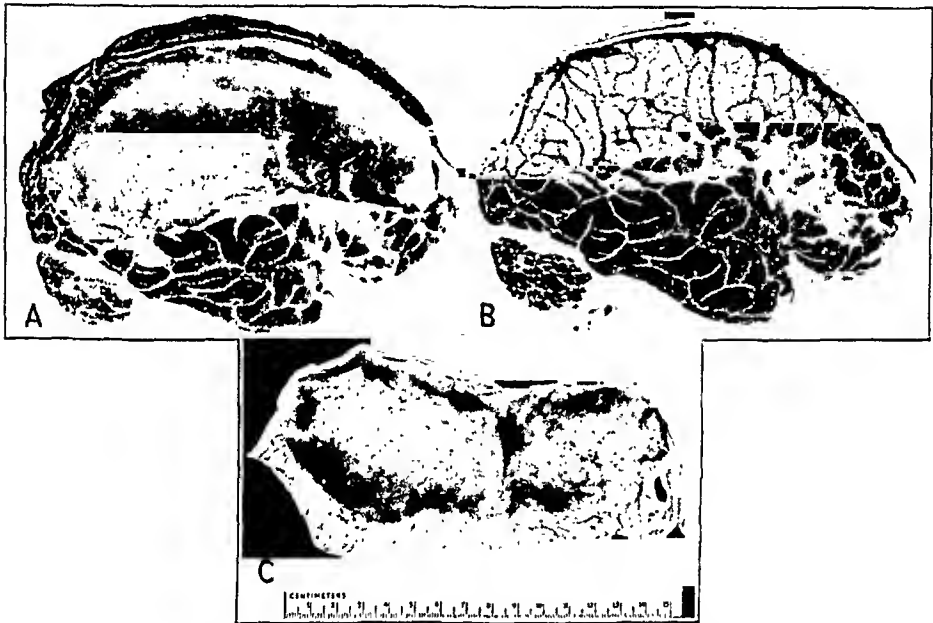


Fig. 1.—*A*, photograph of the brain at autopsy showing an encapsulated subdural hematoma; *B*, the hematoma has been removed, showing the depression of the cortex; *C*, the encapsulated hematoma.

pressure; the fluid is usually clear. Spinal punctures are dangerous in a case of suspected extradural hematoma<sup>2</sup> and are of little or no value in diagnosis other than to reveal a high intracranial pressure.

When the patient is deeply comatose, the breathing becomes deep and slow, with long, drawn out inspirations and a puffing out of the cheeks on expiration. This blowing type of respiration is much like that

1. Dandy, W. E.: Subdural Hematoma, Subdural Hydroma, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, pp. 295-309.

2. Extradural hematoma is synonymous with middle meningeal hemorrhage.

seen in a patient just entering the surgical stage of anesthesia induced with ether. I have never observed this type of respiration in any other type of craniocerebral injury. This characteristic pulse and blowing respiration has in my experience been a valuable aid in the diagnosis of middle meningeal hemorrhage, especially in those instances in which the history was inadequate. The blowing respiration and the full volume pulse were present in 10 of the 25 patients; all 10 were in deep coma.

By far the most important single symptom of progressive intracranial bleeding is a deepening coma.<sup>3</sup> Every patient with a history of head injury, who several hours later goes into a coma from which he cannot be roused, surely has intracranial bleeding.

Another important sign that develops in about half of the patients is a dilated pupil on one side—on the same side as the hemorrhage. The dilated pupil, when present, is of great value in localization, even more so than the motor paralysis. A large hematoma extending over almost an entire hemisphere has been found to produce a shift of the brain with resultant pressure on the brain stem of the contralateral side, giving rise to confusing motor symptoms. The dilated pupil in these instances is of more reliable localizing value than the motor paralysis.

Fourteen of the patients in this series had a dilated pupil, and in 13 of these, the hemorrhage was found on the side indicated by the pupil. In 4 of the patients, the paralysis was present on the same side as the dilated pupil, and in each instance the pupil was the deciding factor in the correct diagnosis, for the hematoma was located on that side.

If the extradural hemorrhage is not removed surgically, the pulse and respiration rates will remain low as long as the medullary centers can tolerate the pressure; but with failure of the medullary centers, the pulse and respiration rates and the temperature will continue gradually to rise until the patient dies. A rising pulse in a comatose patient is a danger sign of a failing medulla. Another important sign of excessive pressure on the medulla is the development of extensor spasms of the extremities known as decerebrate rigidity. In 5 of the patients with middle meningeal hemorrhage decerebrate rigidity developed prior to operation, and none of these recovered.

CASE 1.—A white man aged 58 was struck by an automobile while crossing an intersection. He was accompanied by his wife.

After momentary unconsciousness, he arose and walked unassisted to the curb. He asked his wife what had happened to him since he did not recall being struck. This occurred about 6:30 p. m.

About 8:30 p. m., he complained of a rather severe headache, placed his hand over the left part of the forehead and the left temple and admitted severe pain

3. Dandy, W. E.: *Diagnosis and Treatment of Injuries of the Head*, J. A. M. A. **101**:772-775 (Sept. 2) 1933.



in that region. At 10:00 p. m., he was unable to talk. The family noted twitchings at this time about the right side of the face and the mouth, and shortly thereafter he became unconscious and had a severe generalized convulsion. He could not be awakened after the convulsion. At 11:00 p. m., the family physician arrived and was angry at being called to attend a patient who was virtually dead. He advised them to call the coroner's office. I saw the patient a half hour later, when he was brought to the Los Angeles General Hospital. His condition was critical.

Examination revealed the patient in deep coma, with a pulse rate of 46, a respiration rate of 16 and blood pressure of 180 systolic and 90 diastolic. There was present complete flaccid paralysis of the right side of the body. The respiration was of the characteristic blowing variety; the inspirations were slow and deep, and the expirations were short and forceful. There was a puffing out of the cheeks with each expiration. The Babinski sign was positive bilaterally. The left pupil was greatly dilated. No time was taken for making roentgenograms or spinal puncture.

A subtemporal craniotomy was done on the left side with the patient under local anesthesia induced with 2 per cent procaine hydrochloride. Black tarry blood extruded immediately through the first perforator opening. A large extradural hematoma was found and removed; it extended over the temporoparietal region. The torn middle meningeal artery was found and sealed by electrocoagulation. A fine linear fracture also was found, crossing the meningeal groove. There was no depression of bone. The patient became conscious the following morning and made a good recovery.

#### CHRONIC SUBDURAL HEMATOMA

The type of hemorrhage just discussed is arterial in origin and develops in four to twelve hours after the injury. There is another type of hemorrhage that is venous in origin and therefore much slower in development. This type develops subdurally and may take many weeks or even months to form; it is therefore known as chronic subdural hematoma.<sup>4</sup> Eighteen of the patients in this series had hemorrhage of this type.

This hemorrhage originates from a torn venous sinus or a large cortical vein, entering the longitudinal sinus. This interesting lesion consists of a collection of semiliquid blood in the subdural space and differs from the extradural type in that it becomes encapsulated and is never absorbed. The blood is eventually broken down and the pigment slowly removed until finally, in a hematoma of long duration, an encapsulated collection of clear fluid results. I have observed this

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4. Kunkel, P. A., and Dandy, W. E.: Subdural Hematoma: Diagnosis and Treatment, *Arch. Surg.* **38**:24-54 (Jan.) 1939. Rand, C. W.: Chronic Subdural Hematoma, *ibid.* **14**:1136-1165 (June) 1927. Dandy.<sup>1</sup>

condition in 1 patient with a history of mental symptoms of many years' duration. The capsule in this instance was calcified to the extent that drill and rongeurs were necessary to open it.

These patients may occasionally go on for many years complaining of headaches; frequently mental symptoms develop. In these cases, brain tumor is suspected, even after ventriculographic studies. In 4 of these 25 cases, the diagnosis was made only after ventriculographic studies, and in 3 of these, the subdural blood was discovered through the burr hole made for the ventriculogram.

At operation, the presence of chronic subdural hematoma is a most welcome sight, since it is one of the most benign of the lesions which give rise to the increased intracranial pressure.



Fig. 2.—Roentgenogram of the brain, showing a calcified subdural hematoma. The patient had symptoms of forty years' duration.

#### CHRONIC SUBDURAL HYDROMA

Another interesting intracranial lesion is chronic subdural hydroma.<sup>5</sup> This consists of an encapsulated collection of clear fluid in the subdural space following an injury to the head. Cerebrospinal fluid passes into the subdural space through a tear in the arachnoid membrane; it becomes encapsulated and gives a clinical picture identical with that of chronic subdural hematoma. The correct diagnosis is made only at operation; recovery is usually complete.

CASE 2.—A laborer aged 70 fell over an iron pipe while at work and bruised his left shoulder. He was sent home and returned to work the following morning.

5. Coleman, C. C.: Chronic Subdural Hematoma, *Am. J. Surg.* 28:341-363 (May) 1935. Naffziger, H. C.: Subdural Fluid Accumulations Following Head Injury, *J. A. M. A.* 82:1751-1752 (May 31) 1924. Dandy.<sup>1</sup>

Although he did not feel well, he continued working with interrupted periods of illness for about five weeks.

Five and one-half weeks after the injury, he complained of headaches for the first time. Three days later, he began to limp with his right leg, and within the next two days, he became confused and drowsy and had urinary incontinence for the first time. A few hours later, he became comatose and exhibited a weakness of the entire right side of the body with a positive Babinski sign on the right.

The family physician made a diagnosis of cerebral thrombosis but, not being certain, called Dr. J. P. Fitzgibbon, who made the diagnosis of chronic subdural hematoma. I saw the patient on the same night at the Cedars of Lebanon Hospital. The patient was now in deep coma with complete flaccid paralysis of the entire right side. The pupils were small and equal. The temperature and the pulse and respiration rates as well as the spinal fluid findings were normal.

I operated on the patient the same evening. Massive chronic subdural hematoma was found on the left and chronic subdural hydroma on the right. The patient became conscious in six hours. Recovery was complete.

An acute brain injury is sometimes mistaken for an interval hemorrhage.<sup>3</sup> This type of patient is rendered immediately unconscious and remains so for an indefinite period—many hours or even days. In these patients, a rapid, bounding pulse, rapid moist breathing and a gradual rise in temperature develop early. There is often an associated injury to the midbrain or the pons in these acutely ill patients.

Persons with alcoholism who have received a concussion may, several hours after the injury, become comatose, and a low pulse rate may be present. They seem to fall into a deep sleep for many hours, and if they are permitted to lie flat on their backs, the relaxed tongue falls back and obstructs the breathing; this gives rise to stertorous sounds and at times even resembles the Cheyne-Stokes type. A patient of this type occasionally will have a generalized convulsive seizure. Careful observation, as well as the absence of focal or localizing signs, and history of alcoholic intoxication prior to the injury will aid in making the correct diagnosis.

Figure 2 is used with the permission of Dr. C. B. Courville.

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## SHOCK PRODUCED BY CRUSH INJURY

EFFECTS OF THE ADMINISTRATION OF PLASMA AND THE  
LOCAL APPLICATION OF COLD

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AND

ALFRED BLALOCK, M.D.

BALTIMORE

In a previous paper<sup>1</sup> we described a method for producing experimental shock in which an attempt was made to simulate the crush syndrome in patients. The method consisted in placing a posterior extremity of the anesthetized animal in a mechanical press which had uneven surfaces. It was found that removal of the extremity from the press after five hours was followed by swelling of the thigh, an increase in the concentration of the blood, a decline in blood pressure, oliguria, abnormal urinary findings, elevated blood creatine and creatinuria and usually death. There was a large loss of plasma into and near the crushed area.

Only 1 of 19 animals in which the press was in place for five hours survived, despite the fact that all the animals appeared to be in good condition at the time the press was removed. On the other hand, it was found that 15 of 21 additional animals survived when a pneumatic tube exerting a pressure of 40 mm. of mercury was applied to the extremity immediately following the removal of the press. This was due presumably to a lessening of the local loss of fluid. There was no evidence that the pneumatic tube caused venous obstruction.

The present experiments were carried out in an attempt to prevent by other means the peripheral circulatory failure which follows this type of crush injury. The measures that were used in some experiments consisted in the intravenous administration of blood plasma equal in amount to the average loss into and near the injured area as reported in the

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1. Duncan, G. W., and Blalock, A.: The Uniform Production of Experimental Shock by Crush Injury: Possible Relationship to Clinical Crush Syndrome, *Ann. Surg.* **115**:684, 1942.

previous studies. In other experiments the effects of the local application of ice to the injured area were determined. In some instances the extremity was surrounded with ice during the entire five hour period that the press was in position. In the remaining experiments the extremity was cooled after removal of the press.

#### METHODS AND RESULTS

The method which was used in causing the crush injury was the same as that reported in the previous paper.<sup>1</sup> Several points should be emphasized. Medium-sized dogs, weighing between 7 and 11 Kg., were used in all experiments. Animals were chosen which had a good deal of muscular tissue in the thigh. The press was placed on the thigh in such a manner that the position of the femur corresponded to the groove in the triangular strips of wood. Pain was prevented by the use of anesthesia; the anesthetics were given in the doses which were used in the previous experiments.

*Effects of Injecting Plasma.*—The average difference in the weights of the crushed and noncrushed extremities in our first experiments amounted to 3.3 per cent of the body weight. As stated in our report, 20 of 21 animals in the control nontreated group died after removal of the press. The average survival time was slightly less than eight hours. In the present experiments, the intravenous administration of blood plasma from a second animal was begun immediately after the removal of the press. The plasma was administered slowly over a two hour period in most experiments, the shortest period being one hour. A total of 15 experiments was performed. The decline in blood pressure following removal of the press and during the time that the plasma was being administered was not so abrupt as that observed in the previously reported control experiments. It is to be noted, however, that in several experiments significant declines did occur during this period. An increase in the concentration of the blood was found in all the experiments, but again the alterations were not so great as previously noted in the untreated group. An increase in the pulse rate was found to occur in all experiments. The average elevation of rectal temperature was 2.3 F. These values are given in table 1.

Nine of the 15 animals died at intervals of thirteen to forty hours after removal of the press, the average survival time of this group being twenty hours. Alterations in nonprotein nitrogen, plasma creatine and plasma creatinine and urinary creatine and creatinine were greater in these 9 animals than were the changes in comparable periods in the 6 animals that survived. Similar differences were noted in the two groups on gross and microscopic examination of the urine. The urine of all the animals became grossly bloody within one hour after the press was removed. The urine of animals succumbing in forty hours or less showed numerous red cell casts and granular casts. Only 2 of the animals that survived showed granular or red cell casts, and these were few in number. The studies on the blood and the urine of 2 of the 9 animals that died are given in table 2.

As has been stated, the average difference in the weights of the injured and noninjured extremities in the control nontreated animals equaled 3.3 per cent of the body weight, and it is for this reason that it was decided in the present experiments to give plasma in quantities corresponding to this difference. Following the death of the 9 animals in the present group of experiments, the difference in the weights of the injured and noninjured posterior extremities

was determined by a bisection method.<sup>2</sup> This difference varied from 4.06 to 6.04 per cent, the average difference being 5.33 per cent. If one can assume that the experiments were identical except for the introduction of plasma into the animals of the present group, the figures show that only about two thirds of the plasma which was injected was lost at the site of injury. These figures are given in table 1.

It has been stated that 6 of the animals survived the immediate effects of the crush injury. This group includes 1 animal which died twenty-three days later. The cause of death of this animal was not determined with certainty, but the most significant observations included small amounts of free fluid in both pleural cavities, areas of focal necrosis in the liver and extensive scarring and fibrous replacement of a large part of the skeletal muscle of the thigh. The remaining 5 animals were observed for at least forty days. As stated previously, the changes observed in the blood and the urine were not so great in these 6 animals as in the animals which died within forty hours. The plasma creatine levels showed an average increase of 2 mg. per hundred cubic centimeters at the end of four to six hours and 2.6 mg. per hundred cubic centimeters at the end of twenty-four hours. The plasma creatinine levels had increased 0.3 mg. per hundred cubic centimeters at the end of four to six hours and 0.9 mg. per hundred cubic centimeters at the end of twenty-four hours. Both creatine and creatinine levels in the plasma had returned to normal at the end of forty-eight hours and remained within normal limits throughout the period of observation.

The nonprotein nitrogen levels of the blood of this group of animals showed an average increase of 11.4 mg. per hundred cubic centimeters at the end of four to six hours and at the end of twenty-four hours an average increase of 41.4 mg. per hundred cubic centimeters. Elevation of the nonprotein nitrogen was present in 3 of the 6 animals at the end of forty-eight hours, but all had reached normal levels by the fourth day. Subsequent frequent determinations showed occasional transient elevations of nonprotein nitrogen in all animals during the succeeding thirty-five to fifty days of observation.

The urinary output of these 6 animals at the end of four to six hours averaged 60 cc.; during the remainder of the first twenty-four hours, the average output was 48 cc. The gross hematuria which was present in all animals for the first twenty-four hours had cleared up at the end of forty-eight hours. The urinary output had increased to normal by the end of forty-eight hours and remained within normal limits throughout the period of observation. The urinary creatine and creatinine returned to the range of the control levels by the end of forty-eight hours, and no further elevations were observed.

Extensive injury to the compressed extremity resulted in all 15 experiments. Massive swelling, becoming maximal in six to eight hours, always followed removal of the press. In all experiments, the swelling of the injured extremity of the animals treated with plasma was greater than that of the control untreated animals. Examination of the thigh revealed extravasation of yellow fluid into the muscles, along fascial planes and into the subcutaneous tissues of the extremity and the adjacent body wall. The swelling was later complicated by the presence of either superficial or deep infection of the thigh so that the duration of the swelling due to plasma loss *per se* could not be accurately determined. Five of the 6 animals showed necrosis of the skin with superficial ulceration at the sites

2. Blalock, A.: Experimental Shock: A Cause of Low Blood Pressure Produced by Muscle Injury, *Arch. Surg.* 20:959 (June) 1930.

TABLE 1.—Showing the Effects of Introducing Blood Plasma After Having Caused Crush Injury

Experiment Number	Mean Arterial Pressure, Mm. of Mercury		Hematocrit Reading		Pulse Rate per Minute		Respiratory Rate per Minute		Temperature, F.		Hours Press Was Applied		Therapy	Survival After Press Was Removed	Fluid Loss, per Cent of Body Weight	Examination of the Injured Extremity
	Control	Reading 6 to 8 Hr. After Press Was Removed	Control	Reading 6 to 8 Hr. After Press Was Removed	Control	Reading 6 to 8 Hr. After Press Was Removed	Control	Reading 6 to 8 Hr. After Press Was Removed	Control	Reading 6 to 8 Hr. After Press Was Removed						
1	110	40	35.2	44.3	120	200+	6	14	100.1	103.2	5	Plasma, 3.3% of body weight	Recovered	...		Marked swelling of the thigh, which persisted in the region of the knee joint; patellar reflex absent; posterior dislocation of the knee joint; necrosis of the skin at the site of the teeth of the press; deep infection in the thigh and suppurative arthritis of the knee joint developed
2	120	105	45.6	63.0	160	200+	10	10	99.1	100.8	5	Plasma, 3.3% of body weight	15 hr.	5.97		Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the body wall
3	115	110	54.0	68.0	116	200	6	10	101.3	102.2	5	Plasma, 3.3% of body weight	29 hr., 45 min.	5.21		Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the body wall
4	125	115	48.9	60.7	120	132	8	16	101.3	103.7	5	Plasma, 3.3% of body weight	20 hr., 15 min.	1.76		Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the body wall
5	120	120	48.6	50.7	120	200	8	6	93.5	102.6	5	Plasma 3.3% of body weight	23 days	No swelling at time of death		Marked swelling of the thigh, which persisted approximately 20 days; footdrop present and patellar reflex absent—this persisted until death; ulceration of the skin persisted approximately 20 days; marked fibrosis of muscle of the thigh

6	125	90	40.5	55.4	116	200	12	36	101.6	103.0	5	Plasma, 3.3% of body weight	Recovered	.	Marked swelling of the thigh, which persisted approximately 21 days; necrosis of the skin with ulceration which persisted approximately 10 days; footdrop persisted approximately 31 days; patellar reflex absent 28 days
7	135	125	41.4	49.1	124	172	6	8	100.7	103.2	5	Plasma, 3.3% of body weight	Recovered	.	Marked swelling which persisted 6 to 7 days; patellar reflex absent 11 days; footdrop persisted approximately 14 days; no skin necrosis
8	125	95	40.8	58.4	136	124	6	16	100.2	102.1	5	Plasma, 3.3% of body weight	11 hr.	6.01	Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the body wall
9	140	105	51.8	71.3	116	200	10	10	100.7	100.8	5	Plasma, 3.3% of body weight	11 hr	5.68	Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the body wall
10	125	100	45.4	50.7	112	188	12	10	99.8	103.1	5	Plasma, 3.3% of body weight	Recovered	.	Marked swelling of the thigh; necrosis of a large area of skin with development of infection in this area; marked scarring in the skin and the subcutaneous tissue; absence of the patellar reflex persisted
11	130	90	49.2	73.4	120	200+	8	10	101.1	101.1	5	Plasma, 3.3% of body weight	11 hr	5.51	Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the adjacent body wall
12	125	85	48.5	62.4	112	200+	8	11	99.7	102.2	5	Plasma, 3.3% of body weight	Recovered		Marked swelling of the thigh which persisted approximately 11 or 12 days; necrosis of the skin at the site of the pre-s teeth persisted approximately 17 days; footdrop persisted 21 days; patellar reflex remained absent until death by killing on the fortieth day
13	125	120	45.4	69.0	160	180	6	16	98.5	102.6	5	Plasma, 3.3% of body weight	11 hr	5.35	Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the adjacent body wall
14	120	100	49.7	58.6	136	200+	6	16	101.1	103.6	5	Plasma, 3.3% of body weight	10 hr	1.06	Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the adjacent body wall; swelling was less marked at the time of death
15	130	80	53.7	62.3	130	200+	8	8	99.5	101.2	5	Plasma, 3.3% of body weight	13 hr	5.65	Marked swelling of the thigh consisting of yellow fluid in the muscles, along the fascial planes and the adjacent body wall



where the greatest pressure had been exerted by the wooden teeth of the press. Two of the group had more extensive deep-seated infections of the thigh, and these infections resulted in extensive scarring. Footdrop which persisted for periods varying from fourteen to thirty-four days developed in 4 animals. The presence or absence of footdrop in the 2 animals with deep infections could not be ascertained because of failure to use the extremity in walking. The patellar reflex was absent in all animals—for twenty-eight and thirty-one days in 2 animals and until death or killing in the other 4. One animal sustained a posterior dis-

TABLE 2.—*Urinary and Blood Findings as Affected by Crush Injury and Plasma Therapy*

Experiment Number	Test	Control Reading	Reading After Press Was Removed		Comment
			4-6 Hr.	24 Hr.	
3	Nonprotein nitrogen, mg. per 100 cc.....	34.2	....	98.9	Urine became grossly bloody within one hour after press was removed; microscope examination of the urine following removal of the press showed numerous granular and red cell casts and numerous erythrocytes; the total output of urine following removal of the press was 78 cc.; died after 29 hours, 15 minutes
	Plasma creatine, mg. per 100 cc.....	0.9	....	12.9	
	Plasma creatinine, mg. per 100 cc.....	2.1	....	6.6	
	Hematocrit.....	54.0	64.2	70.0	
	Urine output, cc.....	....	40.0	38.0	
	Gross examination.....	Clear yellow	Bloody	Bloody	
	Urine creatine, mg. per 100 cc.....	0.5	....	2.8	
	Urine creatinine, mg. per 100 cc.....	2.8	....	1.5	
14	Nonprotein nitrogen, mg. per 100 cc.....	21.5	36.0	129.0	Urine became grossly bloody within 1 hour after the press was removed; microscope examination of the urine following removal of the press showed numerous granular and red cell casts and numerous erythrocytes; the total output of urine from the time of removal of the press until death at 40 hours was only 110 cc.
	Plasma creatine, mg. per 100 cc.....	1.4	10.2	13.5	
	Plasma creatinine, mg. per 100 cc.....	1.1	2.3	4.0	
	Hematocrit.....	49.7	54.0	....	
	Urine output, cc.....	....	15.0	23.0	
	Gross examination.....	Clear yellow	Bloody	Bloody	
	Urine creatine, mg. per 100 cc.....	0.9	4.5	3.1	
	Urine creatinine, mg. per 100 cc.....	0.9	0.6	0.6	

location of the knee joint of the crushed extremity, and subsequent development of suppurative arthritis of this joint was observed. Section of the injured thigh of a number of animals revealed extensive scarring and fibrous replacement of a large part of the skeletal muscle.

#### EFFECTS OF THE LOCAL APPLICATION OF COLD

Nineteen experiments with the local application of cold were performed. The results are summarized in table 3.

*Simultaneous Application of Mechanical Press and of Ice.*—In 7 experiments, the extremity was surrounded with ice immediately after application of the press, and this arrangement was maintained during the five hour compression period. Two animals succumbed, the one surviving thirteen hours and the other five

days. At autopsy the lungs of both animals showed findings suggestive of pneumonia. In the animal which died in thirteen hours there was fluid loss into the injured extremity of only 0.59 per cent of the body weight.

Alterations of the criteria under observation in this group were minimal when compared with those observed in the untreated animals previously reported. In 3 of the 7 experiments, arterial pressure declined to 100 mm. of mercury or slightly below; the average fall for the group was 10.7 mm. of mercury. Hemocentration was observed in all experiments but was not marked. The average increase in the pulse rate was 34.6 per minute. The respirations increased in 1 animal, decreased in 4 and remained unchanged in 2. The oral temperature declined in all animals while the ice was on the thigh but returned to approximately the normal level by the end of six to eight hours. In all experiments rectal temperatures were lowered to a greater degree than the oral temperatures because of the proximity of the ice to the rectum.

The 5 surviving animals were observed for at least twenty-three days. Examination of the injured extremity revealed only slight swelling after removal of the press. The injury to the skin and the muscles was not so great as in the untreated animals referred to previously. No severe infections of the injured extremity occurred. In these animals, the urinary output was greater following the removal of the press than it was in the untreated animals or in those animals which survived after treatment with plasma. Gross blood was present in the urine of 2 animals; the urine of all the animals showed erythrocytes on microscopic examination, but in none of the group were casts observed at any time. In 4 animals in which blood nonprotein nitrogen, plasma creatine and creatinine and urinary creatine and creatinine were determined, the changes observed were only slightly above normal values. Subsequent determination of the nonprotein nitrogen showed occasional transient elevations which were unassociated with other evidence of kidney dysfunction.

Although the 7 experiments enumerated are of interest from an academic viewpoint in showing the protective influence of the local application of cold, it is obvious that one cannot thus chill an extremity of the patient who is pinned beneath debris. In order to attempt to approach more closely the conditions which are encountered in the care of patients, other experiments were performed in which the extremity was surrounded with ice thirty minutes after the removal of the press. During this interval a tourniquet was applied to the extremity in order to lessen the early local swelling that follows removal of the press.

*Application of Cold Following Removal of the Press.*—Twelve experiments of this type were performed. In 6 of the experiments, the crushing apparatus was left on the thigh for five hours. On removal at the end of this time, a tourniquet was applied to the upper part of the thigh. Thirty minutes after the press was removed and the tourniquet applied, the extremity was packed in ice. One hour later the tourniquet was removed, the ice being left on the thigh for the ensuing four hours. The remaining 5 experiments were performed in an identical manner except that the crushing apparatus was applied for three and one-half hours instead of five hours.

In the experiments in which the extremity was compressed for five hours before the application of ice, all animals died; the average duration of life was eleven and five-tenths hours. The average fluid loss into the injured extremity was 3.7 per cent of body weight. Three of 5 animals to which the crushing apparatus was applied for three and one-half hours died in an average time of eighteen and three-tenths hours. The average fluid loss into the injured extremity

TABLE 3.—Effects of the Local Application of Cold Coincident with and Following Crush Injury

Experiment Number	Method of Therapy	Mean Arterial Pressure, Mm. of Mercury				Homatocrit Reading		Pulse Rate per Minute		Respi- ratory Rate per Minute		Temperature, F.		Hours Press Was Applied	Survival After Press Was Removed	Fluid Loss, per Cent of Body Weight	Examination of the Injured Extremity
		Control		Reading 4 to 7 Hr. After Press Was Removed		Control		Reading 4 to 7 Hr. After Press Was Removed		Control		Reading 4 to 7 Hr. After Press Was Removed					
		Control	Reading 4 to 7 Hr. After Press Was Removed	Control	Reading 4 to 7 Hr. After Press Was Removed	Control	Reading 4 to 7 Hr. After Press Was Removed	Control	Reading 4 to 7 Hr. After Press Was Removed	Control	Reading 4 to 7 Hr. After Press Was Removed						
1	Extremity packed in ice during the entire period of compression	125	100	49.9	55.4	140	103	10	6	101.8	97.7	5	Recovered	...	Slight swelling of the extremity after removal of the press; no skin necrosis; footdrop persisted 24 days; patellar reflex absent 20 days		
2		120	95	51.0	52.2	124	172	8	10	98.6	101.0	5	Recovered	...	Slight swelling of the thigh following removal of the press; no skin necrosis or ulceration; patellar reflex normal; footdrop persisted 31 days		
3		130	130	53.8	59.4	124	196	10	6	99.2	99.8	5	Recovered	...	Slight swelling of the extremity following removal of the press; no skin necrosis or ulceration; no loss of the patellar reflex; footdrop persisted 24 days		
4		120	120	45.6	50.7	140	178	10	8	100.3	99.8	5	Died, 13 hr.	0.50	Slight swelling of the thigh; pneumonia in both lungs; more marked involvement of the right lung		
5		115	115	50.4	52.6	148	172	12	8	101.0	93.8	5	Recovered	...	Slight swelling of the thigh; no skin ulceration; no loss of patellar reflex; footdrop persisted 28 days		
6		115	105	43.8	44.3	152	160	12	12	99.0	101.2	5	Recovered	...	Slight swelling of the thigh; no skin ulceration; footdrop persisted and patellar reflex was absent at the end of 23 days		
7		115	100	49.7	57.6	96	120	6	6	99.0	98.4	5	Died, 5 days	...	Swelling of the thigh slight and not demonstrable at the end of 24 hours; bloody nasal discharge 3 days before death; patchy pneumonia in the right lung; hemorrhage into the colon and the lower part of the ileum		

8	120	100	43.6	61.4	116	200+	8	12	100.2	91.0	5	Died, 12 hr.	3.75	Moderate swelling of the thigh; yellow fluid in the muscles, along the fascial planes and the adjacent body wall
9	130	100	61.3	81.0	128	158	6	16	98.7	98.6	5	Died, 11 hr.	1.5	Moderate swelling of the thigh; yellow fluid in the muscles, along the fascial planes and the adjacent body wall
15	115	110	48.8	70.5	96	130	10	8	99.1	97.4	5	Died, 12 hr.	1.68	Moderate swelling of the thigh; yellow fluid in the muscles, along the fascial planes and the adjacent body wall
16	115	115	56.0	69.2	108	186	8	10	99.0	97.0	5	Died, 13 hr.	3.12	Moderate swelling of the thigh; yellow fluid in the muscles, along the fascial planes and the adjacent body wall
17	115	70	49.2	71.2	101	150	8	10	99.8	90.0	5	Died, 11 hr.	2.73	Moderate swelling of the thigh; yellow fluid in the muscles, along the fascial planes and the adjacent body wall
18	120	100	53.3	80.1	110	200+	10	6	100.1	92.4	5	Died, 10 hr.	3.21	Moderate swelling of the thigh; yellow fluid in the muscles, along the fascial planes and the adjacent body wall
10	100	85	35.2	51.4	112	200	16	8	102.2	100.2	3½	Recovered	....	Marked swelling of the thigh; later severe deep infection developed in the thigh; patellar reflex was absent and footdrop persisted at 16 days
11	125	115	47.7	68.3	120	132	8	6	100.6	87.0	3½	Died, 5 hr.	3.11	Marked swelling of the thigh; yellow fluid in the tissues of the thigh and on the adjacent body wall
13	115	70	43.0	55.0	112	200+	8	20	101.0	99.0	3½	Recovered	....	Marked swelling of the thigh; deep infection of the thigh and sloughing of the toes and the lateral surface of the thigh developed; footdrop and absent patellar reflex persisted at 9 days
14	120	105	51.1	75.2	124	200+	12	1	99.0	91.0	3½	Died, 40 hr.	2.50	Marked swelling of thigh had diminished some at the time of death; yellow fluid in the tissues of the thigh and the adjacent body wall
15	125	75	56.0	70.2	120	200+	10	10	101.3	93.6	3½	Died, 10 hr.	3.09	Marked swelling of the thigh; yellow fluid in the tissues of the thigh and on the adjacent body wall

was 3.0 per cent of body weight. A decline in arterial pressure was observed in both groups at the end of six to eight hours but was not so great as the decline observed in the untreated control animals. Marked hemoconcentration was observed in all experiments. An increase in the pulse rate occurred in all experiments, the average being approximately the same in the two groups. The body temperature declined in all animals; the average fall in temperature for the two groups was 5.3 F. When observed at corresponding periods after removal of the press, the 2 animals which survived did not show so great a fall in body temperature as did the others.

In all experiments the output of urine was decreased. Grossly bloody urine was observed in all experiments in which the extremity was crushed for five hours. Red cell casts and granular casts were noted in 4 of the 6 experiments. In the experiments in which the extremity was compressed for three and a half hours, gross blood was present in the urine of 3 animals, and granular and red cell casts were observed in only 2.

Swelling of the injured extremity was pronounced in all experiments. In the 2 surviving animals, severe infections of the thigh developed, resulting in extensive scarring. Footdrop and absent patellar reflex were noted in one animal at the end of nine days and in the other at the end of sixteen days.

#### COMMENT

In our previous publication<sup>1</sup> on this subject, attention was focused on the method and on the early effects of the injury. It was stated that practically all the animals subjected to this form of injury die, the average survival time being seven and fifty-five hundredth hours. One of the chief objects of the present experiments was to prolong life for a sufficient length of time in order to observe the animals during the later period which corresponds to that in which oliguria and uremia followed by death have developed in some of the reported clinical cases of crush syndrome. In 6 animals, the injection of plasma prolonged life sufficiently for observation of any similar changes. In these animals a large mass of muscle was crushed, and at least part if not all of the blood supply to an extremity was shut off for five hours. Swelling of the extremity, shock, oliguria, hematuria and the presence of casts in the urine developed after removal of the press, and these alterations simulated fairly closely the essential early features of the reported cases in human beings. In spite of the similarity of these features, the late development of oliguria and casts in the urine and uremia followed by death after several days with the characteristic pathologic findings in the kidneys has not been observed in these experiments. The urinary output of the animals under prolonged observation varied considerably but remained within normal limits. Occasional transient rises in nonprotein nitrogen occurred but were unassociated with oliguria and the presence of casts.

The fluid loss into the injured extremity of the dogs treated with plasma is of special interest when it is recalled that in the untreated control group the local fluid loss into the injured extremity was 3.3

per cent of body weight, whereas in the plasma-treated group the loss was 5.3 per cent of body weight. This observation indicates an additional fluid loss of 2 per cent of body weight into the injured area or almost two thirds of the plasma which was injected. Death resulted in 9 of the 15 animals in spite of the early injection of an amount of plasma equivalent to the average fluid loss which produced death in the untreated animals. Only two thirds of the injected plasma was accounted for, and that was lost locally at the site of injury. It seems likely that the absorption of toxic products played a part in causing the death of these animals.

Trauma to extremities followed by large intravenous infusions of solution of sodium chloride was shown by Harkins and McClure<sup>3</sup> to result in a local fluid loss into the extremity of 6.3 per cent of body weight as compared to an average local loss in traumatized untreated animals of 4.2 per cent of body weight. A local fluid loss of 5.6 per cent occurred in traumatized animals which were given large transfusions of whole blood. In our experiments the fluid lost into the traumatized area was almost entirely plasma. This plasma loss was due to local mechanical injury to the tissues plus the effects of five hours of partial or complete anoxia. The maintenance of the circulating blood volume and of the effective arterial pressure by the injection of plasma was probably responsible for the additional fluid loss into the injured area where gross injury to blood vessels and increased capillary permeability were present. In this connection it is of interest that in other experiments chilling of the part was effective in reducing the local loss of fluid.

The damage produced in the muscles of the thigh could be seen at the time of removal of the press. The muscle bundles were stretched and torn, and in some animals, entire muscles were severed. Late evidence of muscle damage was demonstrated by the extensive fibrosis of all the injured muscles. Necrosis of the skin occurred in most of the animals. In several animals, these areas of skin necrosis served as a portal of entry for organisms producing deep infections of the thigh.

The maintenance of the extremity at a low temperature during the time that the mechanical press was in place exerted a definitely protective influence. This protective influence was probably due to the fact that the metabolism of the tissues was reduced and that less injury resulted from the inadequate blood supply. On the other hand, cooling of the part following the removal of the press did little if any good. Under the latter condition the mechanical injury and the anoxia had already exerted their deleterious effects, and the subsequent lowering of the temperature did not lessen the local loss of fluid or the degree of the other alterations.

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3. Harkins, H. N., and McClure, R. D.: The Present Status of Intravenous Fluid Treatment of Traumatic and Surgical Shock, *Ann. Surg.* **114**:891, 1941.

In several recent additional experiments, the press was left on the extremity for fifteen rather than for five hours. After removal of the press, blood plasma was administered intravenously in an amount slightly in excess of the local loss at the site of injury. These animals succumbed within twenty-four hours after removal of the press. The most likely cause of death in these animals appears to have been the absorption of toxic products from the extremity which had been subjected to gross trauma and prolonged ischemia. The duration of anesthesia is probably an additional factor. Further studies are indicated.

#### SUMMARY

Further studies on experimental crush injuries of extremities are described. Attempts were made to prolong the life of the animals by the injection of plasma equal in amount to the average local fluid loss into the extremities of untreated animals. In spite of this therapy, 9 of 15 animals died with an additional local fluid loss of approximately 2 per cent of the body weight into and about the injured area. The prolonged observations on the surviving animals are described.

The effects of the local application of ice to the injured extremity were studied. In some experiments, the extremity was refrigerated during the entire period of compression, whereas in others the ice was applied after the press had been removed. It was found that cooling of the extremity resulted in less local swelling and an increase in the survival rate if it was maintained during the entire compression period. Lowering of the temperature of the part after the damage had been caused did not appear to exert a favorable influence.

The results indicate that local fluid loss plus the absorption of toxic products was responsible for the death of these animals in which crush injury was produced. When the compression was maintained for several hours only, it was our impression that the local loss of plasma was the major factor in precipitating peripheral circulatory failure. When the compression of the extremity was maintained for many hours and when early death following release of the press was prevented by the administration of plasma, it is likely that the ultimate fatal outcome was due in the main to the effects from the absorption of toxic products.

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## OSSEOSONOMETRY

### I. THE USE OF PERCUSSION-AUSCULTATION IN FRACTURES

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Percussion over one end of a bone will set up audible vibrations that are clearly heard with a stethoscope at the other end. These vibrations are even transmitted through one or more joints and may be carried to distant points on the skeleton. It is usually forgotten in physical diagnosis that bone, the hard tissue, carries audible vibrations farther and more clearly than any solid organ or soft tissue. A simple experiment of listening with a stethoscope over the pubis, while a medial malleolus is struck with the finger, shows the distance a percussion note will be carried through bone and likewise illustrates the normal, distinct, low-pitched resonant note which is heard from bone percussion. This sound has a definite "osteal," almost metallic, quality. Other types of vibrations, such as those set up by a tuning fork or vibrator, also can be heard distinctly.

That other tissues and organs transmit and modify sound waves is well known. The principle of percussion established by Auenbrugger in 1755 and the principle of auscultation introduced by Laennec in 1818 have both proved to be extremely important clinical aids. Since the time of these authors, elaborate and reliable relations have been established between the alterations in sound phenomena and the pathologic changes in tissues and organs. It seems amazing that the same principles have not been widely applied to the clinical study and diagnosis of bone lesions.

This study deals only with fractures in long bones, although interesting changes in the percussion note have been found in other less common lesions. The aim has been to make this report of clinical value in the diagnosis and the treatment of fractures. There has been no thought of replacing the indispensable and extensive use of roentgen rays in fracture work. However, there are numerous occasions when

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From the Department of Surgery, Western Reserve University School of Medicine, and the Fracture Service, City Hospital.



auscultation and percussion are available, when the fluoroscope is not and when even a hospital with x-ray apparatus is miles and minutes distant. The justification for the expense of an ambulance, a roentgen examination and hospitalization for an elderly lady who has tripped on a rug and injured her hip is usually obtained with the percussing finger and a stethoscope.

CASE 1.—M. H., a woman aged 62 years, sustained an intracapsular fracture of the left hip (fig. 1). The diagnosis was made by percussion-auscultation before roentgenograms were taken because of a marked change in the quality of the note and a moderate diminution of the intensity observed in comparing the findings on the two legs. Percussion-auscultation from the patella to the symphysis was carried out on each side. After reduction and impaction and immobilization with a Smith-Petersen nail, the percussion note was almost indistinguishable on the two sides. This case illustrates figure 2.



Fig. 1 (case 1).—Roentgenogram of an intracapsular fracture of the left hip. The diagnosis was made by percussion-auscultation before roentgen examination was made.

Information of great value about an injured extremity can thus be obtained with a minimum of delay and expense. That the examination can be carried out painlessly is appreciated by a patient. The injured extremity need not be moved, although it is necessary to place the uninjured one in a symmetric position for the comparative percussion-auscultation.

Fractures of the extremities lend themselves well to percussion-auscultation because there is almost invariably a normal intact bone available for comparison, and symmetric bony prominences are fairly numerous.

The properties of sound are intensity, quality and pitch. A solid elastic body, such as bone, can be set in vibration by percussion; it will

then tend to vibrate at its fundamental frequency or pitch. This frequency follows acoustic laws and depends on the size, the shape, the weight and the elasticity of each bone. The pitch is governed by the law of similar systems as stated by Kimball:<sup>1</sup> "When two vibrating systems are made of the same material, . . . their periods of vibration are proportional to their linear dimensions." As an example he stated that if one takes two steel bars, one of which has half the dimensions of the other, the smaller will make twice as many vibrations per second as the larger when vibrating in the same manner. The intensity of the sound wave will be affected by the laws of reflection, for in the transmission of sound waves from one medium (bone) to another (hematoma and soft tissue), most of the energy (intensity) goes into the reflected wave.<sup>2</sup> The quality of the wave will be modified in a frac-

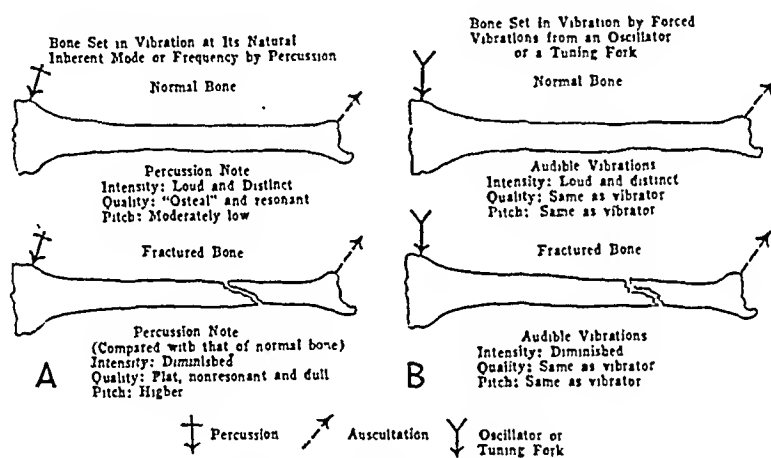


Fig. 2.—Types of vibrations.

ture both by the superficial characteristics of changed pitch and intensity and also by the overtones of the smaller fragments. Thus the ringing resonant quality is usually lost. Although percussion tends to set up a free vibration in bone, it is modified considerably by the dampening effect of soft tissue and muscle in which it is embedded *in vivo*. These primary findings, as illustrated in figure 2 *A*, show the effect of a simple fracture on the intensity, the quality and the pitch of the transmitted percussion note when compared to the note of the normal intact bone.

Solids or bones can be set into vibration also by a tuning fork or a vibrator (fig. 2 *B*). The bone will then be forced to vibrate at the same

1. Kimball, A. L.: College Text-Book of Physics, ed. 2, New York, Henry Holt & Company, 1917, p. 224.

2. Kimball,<sup>1</sup> p. 194.

pitch as the tuning fork. The note heard in the fractured bone will be the same as that heard in the intact bone except that the intensity will be changed. This use of the tuning fork was first described by Andrews<sup>3</sup> in 1903. This was the earliest paper found in a search of the literature on the acoustic phenomena of fractures. In 1929, Polera and Tripodi<sup>4</sup> also elaborated on the use of the tuning fork. They had excellent diagrams, and they described complex variations in the quality of the sound in various fractures. I have been unable to distinguish these variations in quality (fig. 2 *B*) and have found a modification of intensity only. The superiority of the use of percussion over the use of the tuning fork for clinical use will soon become apparent, because all three properties may be changed by a fracture.

The change in the intensity of the percussion note as produced by a fracture was first described by Vigevani<sup>5</sup> in 1925. His method of auscultatory percussion is illustrated in figure 3 and is particularly applicable to bones near the surface of the skin, such as the tibia and

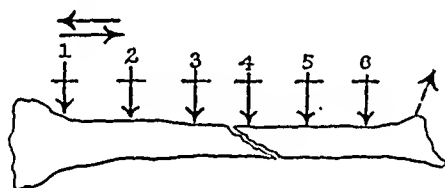


Fig. 3.—Vigevani's method of auscultatory percussion. Percussion is shifted either toward or away from the stethoscope. There is a change in the percussion note between 3 and 4.

the ulna. The stethoscope is held at one end of the bone, and the percussing point is shifted along the bone either toward or away from the listening end. Vigevani described a change in the intensity of the note as the fracture line is crossed by the percussing finger.

CASE 2.—J. L., a man aged 22 years, had a compound comminuted fracture of the right tibia and fibula. There was extensive loss of skin on the medial surface (10 by 3 cm.) ; this wound healed in four months after skin grafting. A Steinmann pin was inserted in the os calcis and then incorporated in plaster. On July 16, 1937 (fig. 4 *A*), a marked change of percussion note was found at the fracture site by the method of Vigevani (fig. 3). On ordinary percussion-auscultation, the intensity was diminished, and the quality was dull and nonresonant when compared to the intact left tibia (fig. 5 *B*). Roentgenograms taken on Jan. 15, 1938, showed

3. Andrews, A. H.: The Tuning Fork and Stethoscope in the Diagnosis of Fractures, Chicago M. Recorder **24**:182-184 (March) 1903.

4. Polera, N., and Tripodi, A.: Diagnosis of Fractures by Phonometry, *Rinasc. med.* **6**:531-533 (Nov., 15) 1929.

5. Vigevani, E.: Auscultatory Percussion in Fractures, *Policlinico (sez. prat.)* **32**:1783-1820 (Dec. 21) 1925.

slight endosteal callus (fig. 4 *B*). There was only slight change in the percussion note. The intensity was only slightly diminished, and the quality was almost normal and resonant (fig. 6 *A*). On May 18, 1940, roentgenograms showed solid healing with a large callus (fig. 4 *C*). The percussion-auscultation intensity was definitely increased over that found in the left tibia (fig. 6 *C*). The roentgenogram was taken because of cellulitis in the leg due to tinca infection in the right foot.

The change in the percussion note of a fractured bone is found to vary markedly according to the type of fracture and the position of the

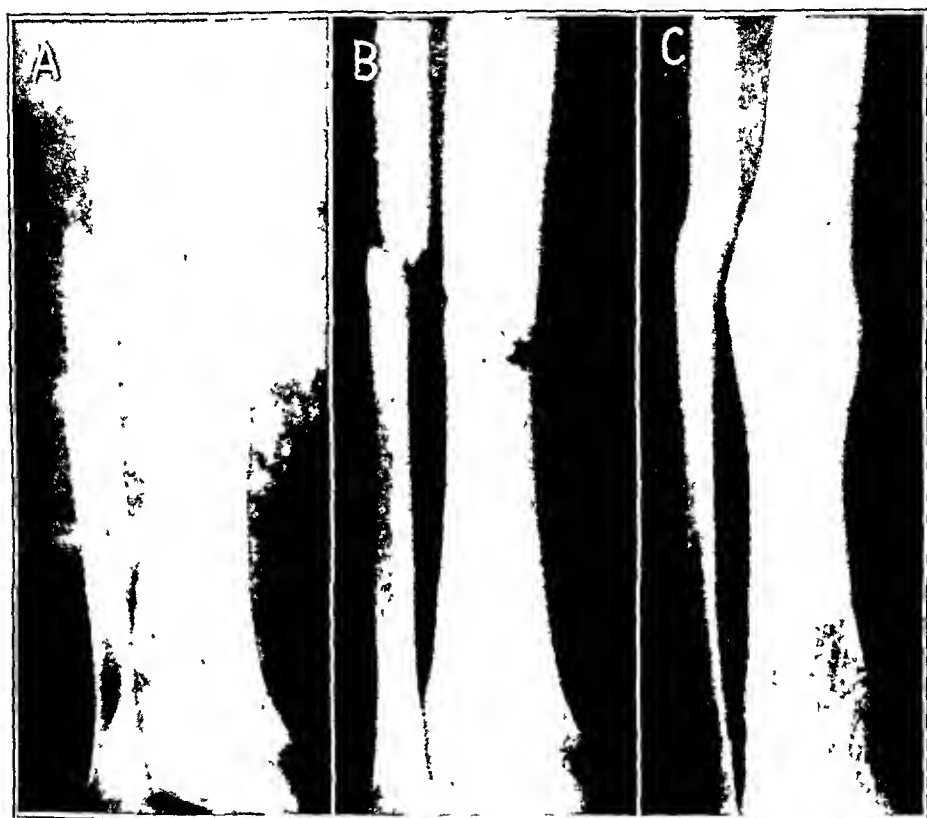


Fig. 4 (case 2).—The patient had compound comminuted fracture of the right tibia and fibula. *A*, roentgenogram taken on July 16, 1937. *B*, roentgenogram taken on Jan. 15, 1938, showing slight endosteal callus. *C*, roentgenogram taken on May 18, 1940, showing solid healing with a large callus.

fragments when percussion-auscultation is carried out. Some of these changes are illustrated in figure 5. The most dramatic change is found in a severely comminuted fracture or in one with overriding fragments (fig. 5 *A*). In fact, if the two major fragments are not in bony contact, no sound at all may be transmitted across the fracture (see initial reading in case 3); this also occurs if there is soft tissue interposition.

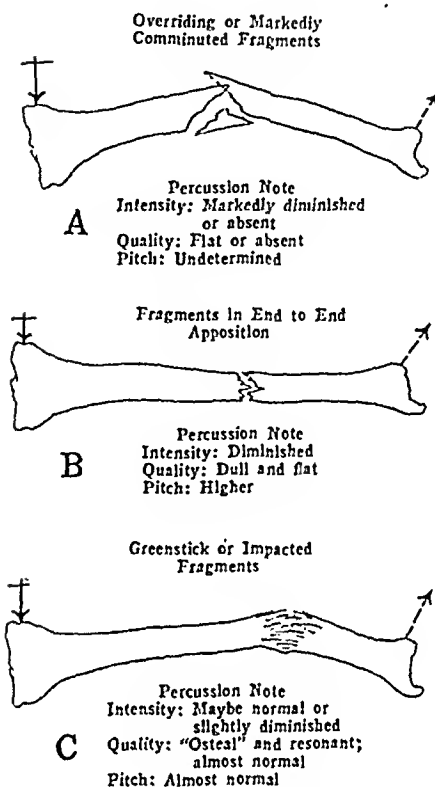


Fig. 5.—Effect of the position of fragments on the percussion note.

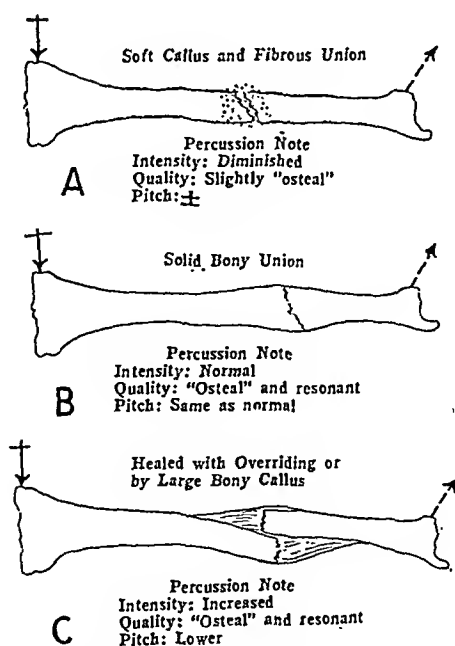


Fig. 6.—Effect of healing on the percussion note.

CASE 3.—I. M., a man, had a compound comminuted fracture of the femur. On admission, a light percussion stroke was not audible on auscultation, and the meter reading was 0. This illustrates the marked effect of a comminuted fracture, as shown in figure 5 *A*. On the next phonometric examination, eight weeks later, the meter reading was  $\frac{1}{4}$ , and the percussion note was now audible owing to the

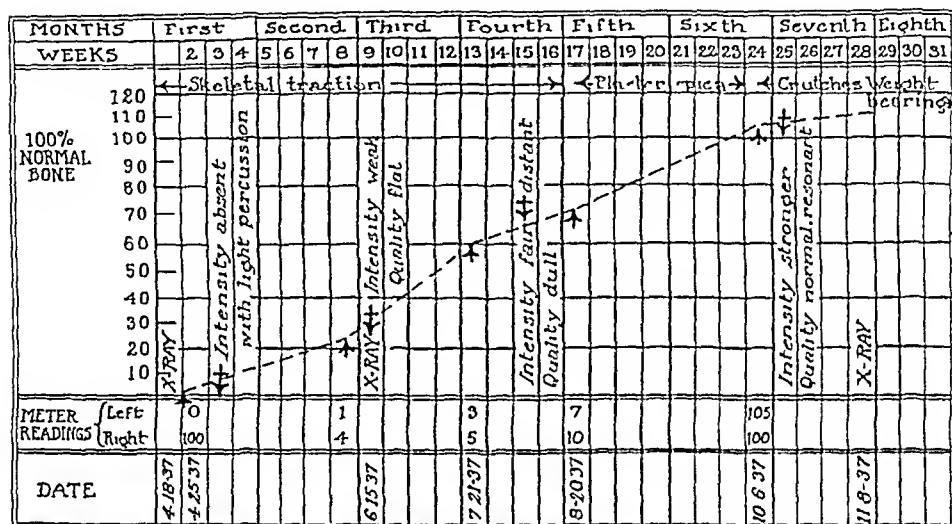


Fig. 7 (case 3).—The patient had a compound comminuted fracture of the femur. On admission, a light percussion stroke was not audible on auscultation, and the meter reading was 0. Eight weeks later the meter reading was  $\frac{1}{4}$ . Later readings disclosed a progressive increase in the intensity of the note to  $\frac{9}{10}$  and then  $\frac{7}{10}$ . After immobilization, the meter readings were all over 100 per cent.

formation of slight intramedullary callus (fig. 6 *A*). Later readings disclosed a progressive increase in the intensity of the note to  $\frac{9}{10}$ , then  $\frac{7}{10}$ , as indicated on the chart in figure 7. Percussion-auscultation showed likewise a gradually increased

intensity of the note. After immobilization in a spica cast, the meter readings were all over 100 per cent, and the note heard on percussion-auscultation of the fractured femur was louder than that heard on percussion-auscultation of the control femur (fig. 6 C). Clinically, the bone was solid, and motion was begun.

This case illustrates how well the percussion-auscultation findings, the meter readings and the roentgen evidence all coincide in the diagnosis and progress of this fracture until healing was obtained.

If an overriding fracture is reduced into good end to end apposition, the intensity of the percussion note is found to be markedly improved over what it was before reduction. This was described by Lippman<sup>6</sup> in 1932, when he advocated auscultatory percussion during the reduction of a fracture. In other words, the better the fragments are reduced, the more nearly normal and intense will be the percussion note.

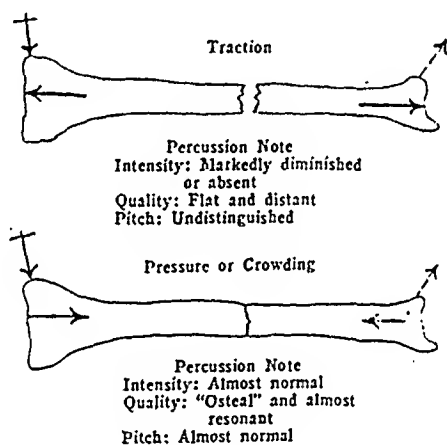


Fig. 8.—Effect of traction or pressure through joints or fragments.

Two types of fractures are extremely difficult of diagnosis by percussion-auscultation. Figure 5 C illustrates these two types. If a fracture is solidly impacted, the whole bone will vibrate as a unit and on auscultation will sound similar to the normal bone. Many greenstick or incomplete fractures fail to give acoustic evidence of fracture for the same reason. Likewise internal fixation, as in the nailing of intracapsular hip fracture, or plating or grafting of fractures, if solidly done, immediately changes the percussion notes so that they sound almost normal. This occurred in case 1 after immobilization with a Smith-Petersen nail.

The effect of traction on a fracture or on a joint during percussion-auscultation is illustrated in figure 8. Traction separating the fragments may completely abolish all transmission of sound. These factors are of

6. Lippman, R. K.: The Use of Auscultatory Percussion for the Examination of Fractures, *J. Bone & Joint Surg.* 14:118-126 (Jan.) 1932.

great clinical value during traction. In making the diagnosis of a fracture, if the signs are not clearcut, traction on both extremities will accentuate or clarify the findings.

CASE 4.—T. L., a man aged 56, had a compound fracture of the lower third of the right femur with a small uninfected puncture wound. A large hematoma developed and was aspirated twice. Skeletal traction of 30 pounds (13.6 Kg.) was applied through the tibial tubercle. On admission, the intensity by percussion-auscultation was markedly diminished and the quality dull (fig. 9 *A*). One week later (fig. 9 *B*) on percussion-auscultation, the note was absent entirely. Diagnosis of overpull and separation of fragments was made by percussion-auscultation before roentgenograms were taken because no sound at all was transmitted through the

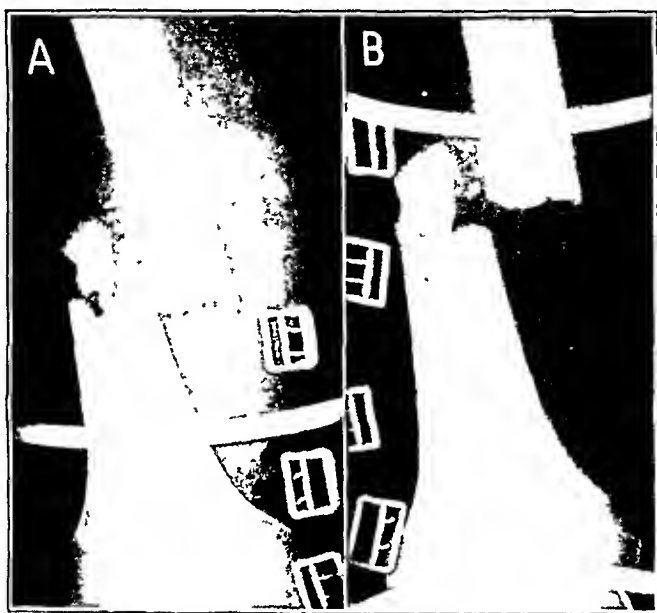


Fig. 9 (case 4).—*A*, roentgenogram taken on March 1, 1941, on admission, showing a compound fracture of the lower third of the right femur. *B*, roentgenogram taken one week later.

femur. Traction was reduced to 15 pounds (6.8 Kg.). The fracture healed with slight overriding.

During this study it soon became apparent that the percussion note in an individual fracture slowly changed as healing and callus formation progressed. These changes are shown in figure 6. As the callus gets stiffer and stronger (fig. 6 *A* and *B*), the percussion note more and more approaches that of the normal bone. It may even, as in figure 6 *C*, surpass the normal bone in intensity if the fracture heals with excessive callus, which may act as a flywheel or pendulum during the vibrations. These changes are illustrated by cases 2 and 3.



This change has been of value in determining the healing of fractures in certain cases. For example, in intracapsular fractures which have not been nailed, the roentgen evidence of healing is not always convincing because little periosteal callus is visible. Percussion-auscultation in these cases may furnish valuable evidence of the degree of healing.

The method in general is shown in figure 10. This illustrates the most convenient bony points for the percussion and auscultation of various bones. It is always advisable to place the uninjured extremity

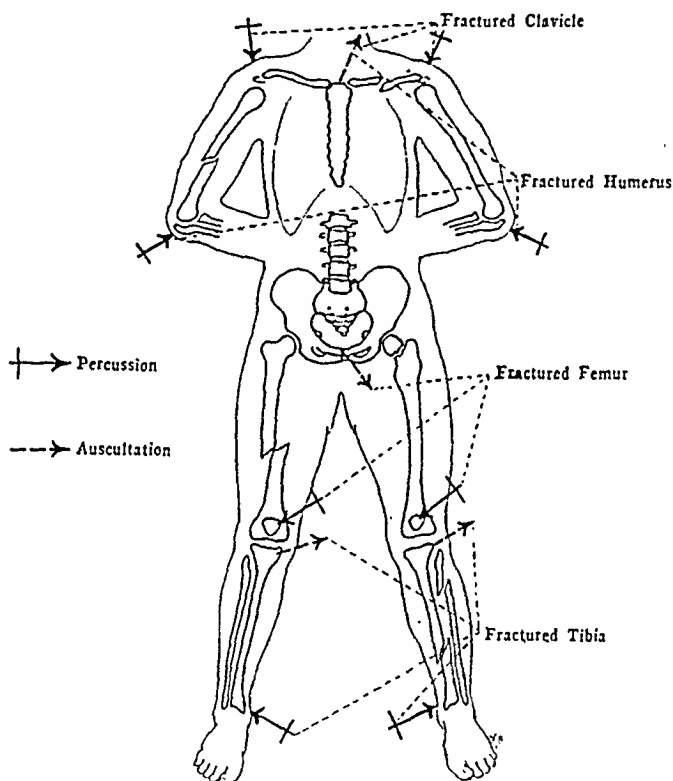


Fig. 10.—Points for percussion and auscultation.

in a symmetric position with the injured one. As stated before, traction on both extremities is sometimes advisable while the injured and control bones are being studied. When percussion and auscultation are used on the proximal long bones, it is always easier to place the stethoscope firmly on a central point, such as the symphysis pubis or the upper part of the manubrium. Then only the percussing finger needs shifting while the bell is held stationary; this eliminates extraneous noises. The clearest signs are elicited when a single bone is compared with its control normal bone. However, if there is much swelling over a percussion point, it is

better to shift to the next distal bony prominence on each extremity since the vibrations are readily transmitted through normal joints. Ordinarily a sharp, clean percussion stroke is used to set a large bone in vibration and to obtain normal resonance. However, a light minimal percussion just audible on the normal bone will at times show slight variations in intensity better than a heavy stroke. Since the distal two long bones in each extremity touch at each end, careful individual percussion must be carried out. The fingers may be studied by lightly tapping the ends and listening over the knuckles with a small bell. However, chip fractures and incomplete fractures cannot be diagnosed. The results are much more satisfactory in the large shaft fractures.

Confidence in this method comes only by experience. By listening to fractures before roentgenograms are made, one soon develops the practice so that it becomes more and more valuable. In percussing each fracture as it comes out of a plaster cast, one soon learns to anticipate the roentgen findings of healing and callus formation.

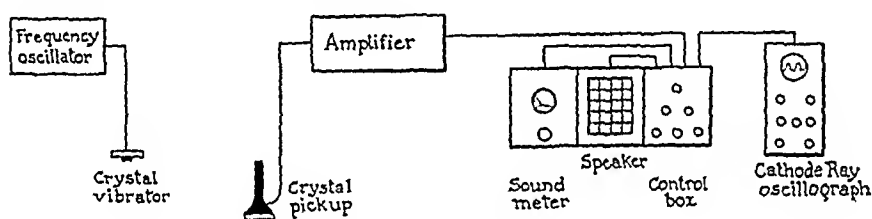


Fig. 11.—Apparatus used in this study.

The apparatus used in this study is shown in figure 11. The intensity or amplitude of the transmitted forced vibration and of the percussion note was thus recorded. This apparatus was frequently used likewise for demonstration before small groups so that the differences in the fractured extremity compared to the normal could be heard and seen. However, it should be strongly stressed that this elaborate apparatus is not at all necessary for clinical use. In fact, one of the virtues of this method of studying fractures is that no apparatus except a stethoscope is needed.

#### SUMMARY

Percussion-auscultation of bone is advocated as an aid in diagnosis, reduction and follow-up of certain shaft fractures, for it is simple, inexpensive and painless.

Changes in the percussion note due to the type of fracture, to the position of the fragments and to the degree of healing are described.

The late A. C. Seletzky, Ph.D., of the Case School of Applied Science, and Mr. John Murray gave assistance in the technical problems involved in this study.

# SOLITARY CONGENITAL (DYSONTOGENETIC) CYST OF THE PANCREAS

REPORT OF A CASE

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AND

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WHITE PLAINS, N. Y.

Solitary cyst of the pancreas has attracted widening interest among surgeons and pathologists, particularly during the last two decades. The number of cases reported in the medical literature testifies to the fact that this condition now must be considered relatively infrequent rather than rare of occurrence. These reports have added to our knowledge of the various clinical pictures of pancreatic cysts as well as of their surgical treatment. We are, however, far from a satisfactory understanding of the pathologic nature and the pathogenesis of these cysts. This deficiency is reflected in the many attempts to obtain a satisfactory classification of pancreatic cyst formation.

On the basis of the histologic picture, the differentiation is generally made between two main groups of pancreatic cysts: (1) true cysts, namely, those characterized by an epithelial lining of the cyst wall; (2) pseudocysts, or those in which an epithelial lining of the cyst wall is lacking.

The majority of pancreatic cysts are pseudocysts. The consensus is that pseudocysts are to be considered the end result of previous pathologic processes taking place in the pancreatic tissues as a result of, for example, inflammatory processes in the gland or that they are caused by external trauma followed by hemorrhages in the gland and the omental bursa.

The so-called retention cyst exhibits epithelial lining of the cyst wall and may be considered a true cyst. In its pathogenesis, however, it appears to resemble a pseudocyst. Pathologic processes in the gland, like pancreatitis or the formation of calculi, may be followed by retrogressive processes which in turn cause obstruction of the free flow of secretion, resulting in retention of secretion in one part of the gland; the inside lining will naturally consist of the epithelium of the now dilated ducts.

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From the White Plains Hospital.

True cysts of other types are rare. They are (a) proliferating cysts (cystic adenoma, cystic epithelioma) and (b) congenital cysts.

Congenital cysts have attracted considerable attention in spite of their rarity for one particular reason, namely, their frequent combination with cysts in the liver, the kidneys, the lungs and the central nervous system. In his classic monograph on cerebellar cysts and angiomas of the retina, Lindau<sup>1</sup> stated that congenital cysts of the pancreas (dysontogenetic cysts) were present in more than half of the recorded cases of this particular condition of the central nervous system. He further concluded that congenital cysts of the pancreas, when encountered in the adult, are associated almost constantly with cysts of the central nervous system.

If substantiated, this concept of Lindau, for obvious reasons, must be of real significance, particularly to the surgeon specializing in abdominal operations. From an investigative point of view, however, it appears that even though in more than half of the recorded cases of pathologic change in the central nervous system dysontogenetic cysts of the pancreas were simultaneously exhibited, the reverse is not necessarily true, that is, the statistical picture might be altogether different when the percentage of central nervous system involvement in cases in which pancreatic cysts are the basis of the statistical material is computed. In order to arrive at a more definite concept of this relation, it therefore seems of some importance to encourage the report of all cases seen by neurologists or neurosurgeons, by surgeons specializing in abdominal operations and by pathologists.

On a previous occasion, Walters and one of us (K.K.N.)<sup>2</sup> reported a case of congenital cysts of the pancreas with partial pancreatectomy. A microscopic study of the removed specimen satisfied the requirements of dysontogenetic cysts of the pancreas. At that time (February 1936), a postoperative neurologic examination of the patient did not reveal any involvement of the central nervous system. A report of the improved condition of the patient, as found on her next and last return to the clinic (August 1936) was included in the report. A later communication from her home physician revealed that during the following year she was progressing well and gaining in weight; the urine remained sugar free and the patient had no digestive disturbances. In August 1937, she was operated on elsewhere because of an acute attack of appendicitis,

1. Lindau, A.: Studien über Kleinhirncysten. Bau, Pathogenese und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. Scandinav., 1926, supp. 1, pp. 1-128.

2. Nygaard, K. K., and Walters, W.: Polycystic Disease of the Pancreas (Dysontogenetic Cysts): Report of Case with Partial Pancreatectomy, Ann. Surg. 106:49-53 (July) 1937.

after which she apparently made an uneventful recovery. About January 1938, or two years after the partial pancreatectomy, she had noted the onset of general weakness, a sensation of epigastric fulness and some increase in the size of the remaining abdominal tumors. There were no further reports of the patient's condition until she died during the latter part of 1938.<sup>3</sup>

We have recently had an opportunity to see a patient who presented a picture similar to that in the case just mentioned, in that no pathologic changes of the central nervous system were demonstrable. The pancreatic cyst, however, was unilocular and obviously of a different category than the polycystic formations, although the condition in both cases was evidently congenital. For these reasons a brief communication is of interest.

#### REPORT OF CASE

A woman 35 years of age was first seen by us on June 25, 1941. About four or five weeks previously, on placing her hand over the upper part of the abdomen, she felt a movable lump under the left costal margin. She did not know whether it had been present long since she never before had had any symptoms referable to the abdomen and had never had a careful physical examination. After she had noted the abdominal lump she occasionally felt a slight soreness or dragging sensation in the upper part of the abdomen, particularly on changing from side to side while recumbent. After detecting the lump, she had not noted any increase in its size. Aside from this information, her past and present history was not significant.

*Physical Examination.*—The patient was of the asthenic type; she was rather high strung but appeared to be in good general condition. Her blood pressure was 110 systolic and 86 diastolic. With the patient in the recumbent position, a moderately large rounded prominence was noted in the upper left quadrant of the abdomen. Dulness was present over this area. Palpation revealed an intra-abdominal tumor, well circumscribed, not tender and freely movable from side to side but less so in the longitudinal axis of the body. The tumor also moved moderately with respiration. When the patient lay on her right side, the tumor could be felt to the right of the midline. At the same time, she experienced a dragging sensation deep in the left upper quadrant of the abdomen. The physical examination otherwise gave essentially negative results.

*Laboratory Investigation.*—The concentration of hemoglobin was 12 Gm. per hundred cubic centimeters of blood. Erythrocytes numbered 4,400,000 and leukocytes 8,000. The differential count was normal; urinalysis also gave normal results. In the complement fixation tests for syphilis, a titer of more than 10 was obtained. An excretory urogram revealed moderate ptosis of the right kidney; the left kidney was in normal position. Otherwise, the outlines of the kidneys, the kidney pelves and the ureters were normal, with good excretion of contrast medium on both sides after five minutes.

The preoperative diagnosis was cyst of the mesentery, omental cyst or pancreatic cyst, in the order mentioned.

*Operation.*—An exploratory laparotomy was performed on July 1 by one of us (K. K. N.). Palpation of the right and left kidneys did not reveal cysts. In the

3. Walters, W.: Personal communication to the authors.

dome of the liver, four small cyst formations were noted, the largest of these measuring 5 mm. in diameter.

The palpable tumor was protruding behind the gastrocolic ligament as well as behind the transverse mesocolon. Because of its intimate contact with the larger vessels of the transverse mesocolon, the tumor was exposed through an opening

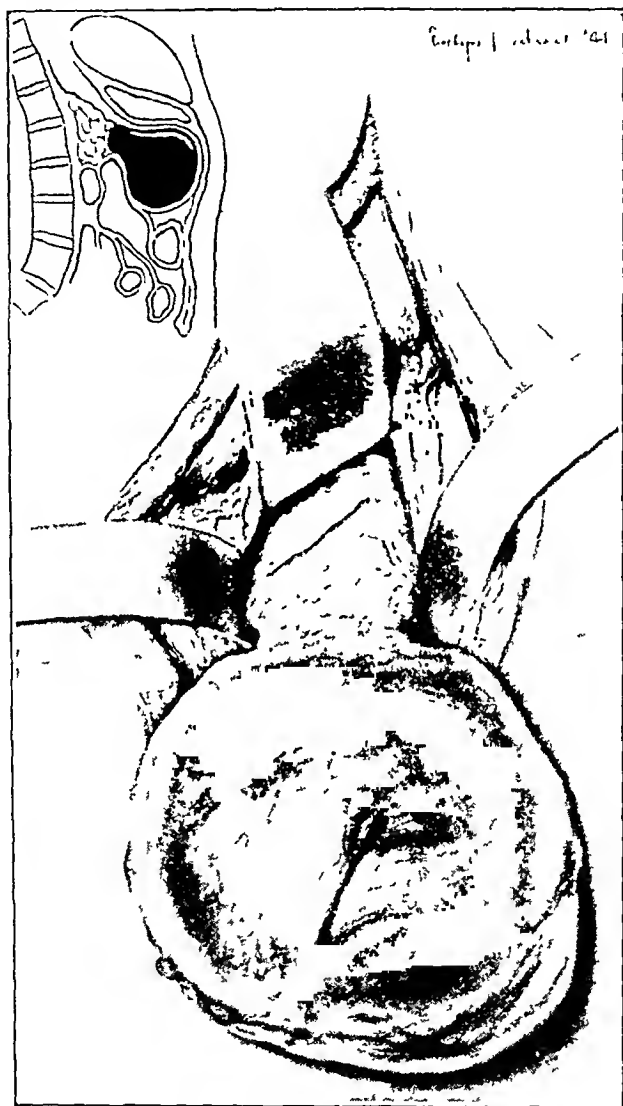


Fig. 1.—Drawing illustrating a pancreatic cyst originating from the lower border of the pancreas. In the inset is shown the operative finding in the sagittal section.

made in the gastrocolic ligament. It was dissected free from its connection with the transverse mesocolon. The tumor was fluctuating. It originated with a rather broad pedicle of normal-appearing pancreatic tissue from the lower border of the body of the pancreas (fig. 1). By careful dissection of its pedicle, it was possible

to peel the intact cyst out of its connection with the pancreatic tissues, leaving a concave area in the pancreas into which the base of the cyst could be fitted like an egg into an eggcup. The bleeding points of the glandular tissue were carefully clamped and tied with silk sutures. Exploration of the pancreas did not reveal the presence of other observable or palpable pathologic processes. Exploration of the other abdominal organs revealed nothing of essential importance. The opening in the gastrocolic ligament was closed around two Penrose drains, inserted down to the area of dissection to prevent the accumulation of the unavoidable postoperative secretion of pancreatic tissue juices.

*Pathologic Report.*—The intact cyst measured 7 by 8 by 8 cm. and weighed 193 Gm. It was unilocular and contained pale yellow clear fluid. The wall of the



Fig. 2.—Photomicrograph of the cyst wall showing the internal lining composed of a single layer of low cuboid epithelium with a single layer of columnar epithelium covering a teatlike projection in a papillomatous area. Note the pancreatic tissue in the lower left corner.

cyst was 0.5 mm. thick. Its inner surface was smooth with the exception of a teatlike projection 3 mm. in diameter and 4 mm. long.

Microscopic examination showed that the cyst wall was formed by stretched connective tissue lined by a single layer of cuboid epithelial cells, except that the filiform projections in the papillomatous area were covered with a single layer of columnar epithelium. Corresponding to the part of the cyst attached to the pancreatic pedicle were areas of pancreatic tissue that contained scattered islands of Langerhans, all of which appeared normal (fig. 2). Chemical investigation of the cyst fluid revealed a diastatic activity of 5,333 units and a tryptic activity of 100 units (Gross' method) as well as lipase.

*Postoperative Course.*—The patient's immediate reaction to the operation was moderate and her further course uneventful. During the first postoperative week,

drainage from the wound had a mild digestive activity on the skin surrounding the drains. These were removed on the ninth postoperative day, and the wound had entirely healed with no further drainage after the sixteenth day.

A dextrose tolerance test performed two weeks after operation gave essentially normal results. In view of the nature of the cyst, a careful neurologic examination was performed before the patient left the hospital. No pathologic changes of the central nervous system could be found. Up to the time of writing, her further course has been satisfactory. Antisyphilitic treatment was started as soon as she had recovered sufficiently from the operation.

#### COMMENT

In most cases of cysts of the pancreas, the whole diagnostic armamentarium of the clinician has to be mobilized. Only in this way may it be possible for him to arrive at an accurate diagnosis which will enable the surgeon confidently to plan a surgical approach and which will enable both to form an opinion of what may and may not be expected from the operation so far as its therapeutic results are concerned. Three types of symptoms should be kept in mind, namely: (1) symptoms referable to the presence of the intra-abdominal tumor; (2) symptoms referable to the presence of pathologic processes which in turn have led to the formation of pancreatic cysts (trauma with hemorrhage into the omental bursa, pancreatitis, cholecystitis, cholelithiasis), and (3) coincidental symptoms caused by independent pathologic processes in the other abdominal organs. In the presence of dysontogenetic cysts, a fourth type of symptoms also should be kept in mind, namely, symptoms referable to cyst formations in other intra-abdominal as well as extra-abdominal organs.

In the present case, this diagnostic difficulty was in no way illustrated. With the verification of the presence of an intra-abdominal tumor without other significant symptoms, exploratory laparotomy suggested itself.

The free mobility of a tumor in the upper part of the abdomen admittedly does not preclude the presence of pancreatic cysts. In 47 cases reported by Judd and associates,<sup>4</sup> free mobility was encountered in 11 of the cases, with 9 of these originating in the tail of the pancreas. In our preoperative discussion of the diagnosis, we placed pancreatic cyst as the last of the likely possibilities because of the extreme mobility. The operative findings satisfactorily explained this sign.

The real interest in the present case centers on the pathologic nature of the cyst. The presence of all three enzymes, namely, diastase, trypsin and lipase, together with the operative findings, indicates the pancreatic origin of the cyst. The endothelial lining indicates the true cystic nature. The absence of other observable or palpable pathologic changes of the pancreas seems to exclude the possibility of a retention cyst.

4. Judd, E. S.; Mattson, H., and Mahorner, H. R.: Pancreatic Cysts: Report of Forty-Seven Cases, *Arch. Surg.* **22**:838-849 (May) 1931.



Finally, the simultaneous formation of cysts in the liver coupled with the deductions already made favors the assumption that we had here a type of dysontogenetic cysts localized in the pancreas and the liver. Recalling the positive serologic test for syphilis, it seems difficult to picture these findings resulting from latent syphilis.

The dysontogenetic cysts of the pancreas are described as having a characteristic histologic picture. Smaller or larger cysts are distributed throughout the entire gland without circumscribed localization. The interstitial tissue is greatly increased, thereby reducing the parenchymatous tissues which otherwise exhibit a normal picture with intact islands of Langerhans. The cyst wall is lined with cuboid epithelium, except in areas with cylindric cells covering papillary proliferations of the cyst wall protruding into the lumen of the cyst.

On the basis of this characteristic picture, earlier pathologists (Wegelin, Yamane, Priesel)<sup>5</sup> conceived the origin of these cysts as a developmental anomaly. For this reason, the growths were termed dysontogenetic cysts. According to Yamane, the earliest developmental anomaly led to isolation of small pancreatic ducts, which partly by retention of glandular tissue secretion, partly by uncoordinated growth of the epithelium, subsequently gave rise to multiple cyst formation. It is of interest to note that the theory of cyst formation implies the polycystic nature of the developmental anomaly.

In one essential respect the cyst reported did not correspond to the characteristic picture of dysontogenetic cysts. It was a solitary unilocular cyst and was not polycystic. In this connection, it is of interest to note that Gruber<sup>6</sup> admitted the rare finding of solitary unilocular dysontogenetic cysts. It is further to be noted that with regard to the microscopic picture of its endothelial lining, the present cyst exhibited a picture identical to that of the individual cyst of polycystic formations. Finally, the simultaneous cyst formations in the liver have to be kept in mind. It is of significance to note that Ledebur<sup>7</sup> many years ago maintained that the developmental origin of polycystic disease of the pancreas could be considered definite only in case of simultaneous cysts in the liver or the kidneys. Although this contention subsequently has been refuted, such a multiple localization of cysts, when present, constitutes added evidence of its congenital origin. In conclusion, therefore, it seems justified to report this present case as representing an unusual type of dysontogenetic cyst located in the pancreas and the liver.

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5. Wegelin, Yamane and Priesel, cited by Lindau.<sup>1</sup>

6. Gruber, G. B.: *Pathologie der Bauchspeicheldrüse (Mit Ausnahme der Langerhansschen Inseln und der Diabetesfrage)*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 5, pt. 2, pp. 211-621.

7. Ledebur, cited by Gruber.<sup>6</sup>

# MANAGEMENT OF RUPTURE OF THE UTERUS

## REPORT OF FORTY-FOUR CASES

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Of the complications of pregnancy and labor, rupture of the uterus is one of the most dangerous.

The object of this communication is to present what informative data are available from a study of 44 patients with rupture of the uterus treated in the Peiping Union Medical College Hospital. This study is especially concerned with the treatment of this condition. Although the available literature has been consulted, an exhaustive review is not attempted. The case histories, illustrative of conditions of obstetric practice in this part of the world, are reported briefly.

Some problems, such as those caused by osteomalacia, which although common here, is rare elsewhere, are peculiar to this region. One may gain an impression also of the obstetric problems arising in a community in which many of the deliveries are attended by untrained midwives without the slightest idea of asepsis or of the mechanism of labor. Through the years there has been a gradual and definite decrease in the mortality rate for those treated for rupture of the uterus in the Peiping Union Medical College Hospital; after analysis of our material, certain factors seem to stand out to explain the improvement. These are: improvement in the availability of blood for transfusion; uniformity in the surgical management in these cases; the benefit of chemotherapy; the advantages of decompression of the gastrointestinal tract, when indicated, by continuous suction on the principle of the Wangenstein apparatus.

Estimates of the frequency of this condition are misleading. There were only 8 instances of rupture of the uterus in this hospital from 1922 to 1934; these were reported by Eastman<sup>1</sup> and Wang.<sup>2</sup> There were 44 of these accidents from 1934 to July 1941. This marked increase in the hospital incidence is probably due to the growing willingness of

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1. Eastman, N. J.: *Am. J. Obst. & Gynec.* **11**:500, 1926.

2. Wang, A.: *Nat. M. J. China* **21**:121, 1935.

the general population to accept hospital treatment. Since there were 52 patients in all with rupture of the uterus among 11,500 obstetric admissions in the history of this department, the incidence in this hospital is 1 in 220. If only the years 1934 to 1941 (the time during which the 44 cases hereinafter reported occurred) are considered, the frequency is 1 in 95. Only 6 of these accidents occurred among our own antepartum patients, while 38 were accepted as emergency cases. The incidence in reports from American and European hospitals varies from 1 in 255 deliveries to 1 in 2,000. We are reporting the highest incidence of this condition that has come to our attention.

Deductions as to the frequency in relation to the number of deliveries in the community are unsatisfactory; this can be said of much statistical data obtained from hospitals admitting many emergency cases.

All of these women unless otherwise indicated were Chinese.

#### RUPTURE OF THE UTERUS DURING LABOR DUE TO MATERNAL CAUSES

##### RUPTURE OF THE UTERUS DUE TO A CONTRACTED PELVIS

CASE 1.—C. L. P., aged 41, a septipara in her eighth pregnancy with the expected date of confinement in June 1935, was admitted on July 1 in labor of five hours' duration. She had been examined repeatedly by a midwife. The patient had had symptoms of osteomalacia since her fifth pregnancy, six years previously. All previous deliveries had been spontaneous and easy. On admission, the patient was in shock and the fetal heart was not heard. The abdomen was tender, and the pelvis was deformed by osteomalacia with a transverse outlet of 6.5 cm. Rupture of the uterus was evident. When the abdomen was opened, the fetus and the placenta were in the abdominal cavity, and a tear which extended through the left broad ligament and the vaginal wall was found in the lower uterine segment. Subtotal hysterectomy was done, and a blood transfusion was given during the operation. The condition of the patient was poor during the operation, but recovery was uneventful, and she was discharged on the twentieth day in good condition.

CASE 2.—C. W. H., aged 19, was admitted in her first pregnancy on Feb. 15, 1936, three weeks from term with ruptured membranes. She had been in labor for three days. The patient had been examined repeatedly by a midwife. Regular labor pains had stopped for twenty-four hours. On admission, the patient was in shock with vomiting and air hunger, and the abdomen was rigid and tender. No fetal heart was heard. The pelvis was markedly deformed by osteomalacia with a transverse outlet of 3 cm. When the abdomen was opened, free blood gushed out. The uterus was ruptured across the anterior portion of the cervix through the right broad ligament, and the shoulder of the fetus protruded through the tear. Subtotal hysterectomy was done. A blood transfusion was given during the operation, but the patient died seven hours later.

CASE 3.—C. S. K., aged 20, a secundipara in her third pregnancy, was admitted on March 8, 1937, two weeks from term, in labor of thirty hours' duration. She had been examined by a midwife. The first baby had been born spontaneously; the second had been delivered with difficulty by breech extraction three years

before admission. The patient had had symptoms of osteomalacia for three years. On admission, the abdomen was tender; the cervix was fully dilated. The fetal parts were felt superficially; the heart tones were not heard. The pelvis was deformed by osteomalacia. At operation, the placenta and the fetus were found in the abdominal cavity. There was a rupture of the uterus from the anterior vaginal fornix extending transversely to both sides. Subtotal hysterectomy was done. She died on the eighth day after a stormy postoperative course.

CASE 4.—W. L. C., aged 32, a secundipara in her third pregnancy, was admitted two weeks from term on July 8, 1937, in labor of thirty-five hours' duration. The membranes were ruptured, and regular labor pains had ceased for eighteen hours. She had been examined by a midwife. The patient had had symptoms of osteomalacia for three years. Previous deliveries were spontaneous and easy; the last had been four years before. On admission, the patient looked extremely sick and had constant abdominal pain. The pelvis, the spinal column, the chest and the extremities were markedly deformed by osteomalacia. No fetal heart was heard; the fetal parts were felt superficially. There were signs of generalized peritonitis. Subtotal hysterectomy was done; about 1,000 cc. of blood was removed from the abdominal cavity, and a blood transfusion was given. The uterus had been torn in the right lower segment, and one fetal arm and shoulder protruded into the abdominal cavity. She died nineteen hours after admission. Autopsy showed generalized peritonitis and streptococcic septicemia.

CASE 5.—P. C. C., a chondrodystrophic dwarf aged 33, was admitted in her first pregnancy on Nov. 5, 1937, one week past term, after being in labor for twenty hours and with rupture of the membranes for twelve hours. She had been repeatedly examined by a midwife, and there had been a sudden sharp abdominal pain with stoppage of regular labor pains and fetal movements. On admission, the patient was in shock, and the abdomen was tender. The fetal parts were felt superficially, and no fetal heart was heard. Vaginal examination revealed a uterine tear over the left side. The patient had a flat pelvis, and the diagonal conjugate diameter measured 10.5 cm. When the abdomen was opened, a moderate amount of blood was present in the peritoneal cavity, together with the baby and the placenta. The tear extended from the left vaginal fornix through the left broad ligament. Subtotal hysterectomy was done. The patient had a septic postoperative course with paralytic ileus and pulmonary complications which terminated in death on the eighth day.

CASE 6.—Y. Y. H., aged 37, a quartipara in her fifth pregnancy, was admitted on Feb. 24, 1938, at term. The membranes had ruptured spontaneously; this was followed by prolapse of a fetal arm. The patient replaced the arm herself, but after eight hours of labor, the arm again prolapsed, and she came to the hospital. On admission she was found to have a generally contracted pelvis with a diagonal conjugate diameter of 10.25 cm. The fetal heart was not heard. Decapitation was done; after this an incomplete transverse tear in the anterior wall of the lower uterine segment was found. The uterus was packed and a blood transfusion given. The family insisted on taking the patient home, and she died the following day.

CASE 7.—Y. S. T., aged 24, a secundipara in her third pregnancy, was admitted at term on June 21, 1938, after a labor of eleven hours and with rupture of the membranes of five hours. She had been examined by a midwife. She had a history of osteomalacia of six years' duration, and the previous labors had been difficult. On admission, the patient was in shock; the fetal head was above the pelvic inlet,

and the heart tones were absent. The pelvis was deformed by osteomalacia. Vaginal examination was done, and a tear over the lower uterine segment toward the right was found. A blood transfusion was given before the operation. When the abdomen was opened, the baby and the placenta were free in the peritoneal cavity. There were signs of peritonitis. The rupture was in the lower uterine segment and involved the right side and the whole anterior surface. Subtotal hysterectomy was done, and another transfusion was given. The patient died five hours after the operation. A postmortem blood culture demonstrated the colon bacillus.

CASE 8.—L. C. H., aged 27, a tertipara in her fourth pregnancy, was admitted on June 18, 1939, two weeks past term. She had been in labor for twenty hours; the membranes had ruptured, and the cord was prolapsed. She had been examined by a neighbor. The first child had been born spontaneously. The second labor was prolonged and was terminated by a destructive operation done by a midwife. The third child was stillborn. On admission, the patient was in shock; the abdomen was tender, and the fetal heart was not heard. The pelvis was deformed by osteomalacia, with a transverse outlet of 7 cm. and a diagonal conjugate diameter of 9 cm. The baby was delivered by breech extraction. Vaginal examination done after delivery revealed a rupture of the uterus. At operation, the uterus was found torn anterolaterally toward the left. Subtotal hysterectomy was done. A blood transfusion was given during, and another after, the operation. The postoperative course was uneventful, and the patient was discharged twenty-six days later.

CASE 9.—W. T. M., aged 28, a secundipara in her third pregnancy, was admitted at term on Sept. 3, 1939, after being in labor for sixty hours and with rupture of the membranes for four days. The labor pains had stopped, and the patient had been mentally cloudy for ten hours. Attempts by a midwife to bring about delivery had been unsuccessful. The first two deliveries had been spontaneous; the last of these was four years before admission. She had had bone pains for three years. On admission, the patient was in shock; the uterus was in tetanic contraction, and no fetal heart was heard. The pelvis was deformed by osteomalacia, with a transverse outlet of less than 6 cm. Craniotomy was done with great difficulty. The uterus was later found to be ruptured, and a blood transfusion was given before the operation. At operation, the uterus was found torn on the left side up to the broad ligament. Subtotal hysterectomy was done. The patient died four hours after admission.

CASE 10.—L. H. W., aged 22, a secundipara in her third pregnancy, was admitted at two weeks from term on Nov. 11, 1939, after being in labor for three days with rupture of the membranes for thirty-three hours. The patient had been examined repeatedly by a midwife. Labor pains had stopped for eight hours, and the patient had become mentally cloudy and restless. Her history suggested that she had had osteomalacia for the past four years. On admission, the patient was in a moribund state. Material with the appearance of coffee grounds flowed from the mouth. The fetal parts were felt superficially, and shifting dulness was demonstrated. No fetal heart was heard. Generalized tenderness was present over the abdomen. The pelvis was deformed by osteomalacia. Dextrose infusion followed by a blood transfusion was given. Flatus escaped when the abdomen was opened. The baby was on top of the uterus, which was torn anteriorly over the lower uterine segment. The posterior wall of the bladder was completely torn. There were extensive

peritonitis and paralytic ileus. Subtotal hysterectomy was done, and no attempt was made to repair the bladder because of extensive necrosis. Another blood transfusion was given after the operation. The patient died eleven hours after admission. At autopsy acute general peritonitis was found.

CASE 11.—S. K. L., aged 29, a quartipara in her fifth pregnancy, was admitted ten days before term, on Nov. 24, 1939, after being in labor for fifteen hours without making progress. The patient was referred here from another institution because of an attack of severe pain an hour prior to admission. On admission, the patient was in shock; the fetus was in the abdominal cavity, and the pelvis was deformed by osteomalacia. At operation, free blood, the fetus and the placenta were found in the peritoneal cavity. The rupture of the uterus was on the right side in the lower uterine segment. Subtotal hysterectomy was done, and a blood transfusion was given during and after the operation. The postoperative course was stormy; the abdominal wound was infected, and a pelvic abscess developed, which was drained. The patient recovered and was discharged forty-four days after the operation.

CASE 12.—J. K. M., aged 33, a primipara in her second pregnancy, was admitted a week from term, on July 12, 1940, after being in labor for eleven hours. The patient was referred here from another institution. The membranes had ruptured spontaneously six hours before admission. A vaginal examination had been done by a physician at the other institution, and the fetal head was found to be floating above the pelvic inlet in spite of the strong uterine contractions. On admission, the fetus was in left occipitoanterior position with the presenting part above the spines. The fetal heart tones were good. The cervix was 6 to 7 cm. dilated, and the uterine contractions were strong. The patient was found to have a generally contracted pelvis with a diagonal conjugate diameter of 10 cm.; the transverse outlet measured 6.5 cm. When the abdomen was opened, a partial rupture of the uterus was found with two large subperitoneal hematomas, one on each side of the uterus. Subtotal hysterectomy was done, and the baby lived. A blood transfusion was given after the operation. The postoperative course was uneventful, and the patient left the hospital after twenty days.

#### RUPTURE OF THE UTERUS THROUGH AN OLD CESAREAN SECTION SCAR

CASE 13.—K. H. J., aged 34, a primipara in her second pregnancy, was admitted on Sept. 11, 1934, six weeks before the expected date of confinement because of sudden acute abdominal pain followed by collapse. She had undergone a classic cesarean section in this hospital in 1931 because of a generally contracted pelvis; the postoperative course had been febrile. On admission, the abdomen was tender, but the patient's condition was relatively good. At operation the shoulder of the baby was found to be protruding through the old uterine scar. The baby was delivered in good condition, and the tear was repaired. The patient was discharged in good condition in twenty days.

CASE 14.—U. L., a Russian housewife aged 30, a primipara in her second pregnancy, was admitted on Nov. 2, 1940, two weeks before the expected date of confinement. She had had a classic cesarean section in 1938 in another hospital because of abruptio placentae. The abdominal wound was badly infected but healed in three months. On admission, the patient had been in labor for twenty-four hours and had ceased to make progress. There was some abdominal pain, and operation

was decided on. When the abdomen was opened, a rupture through the old scar was found. The dead fetus was extracted, and subtotal hysterectomy was done. The patient left the hospital in fifteen days after an uneventful course.

CASE 15.—L. L. C., aged 33, a secundipara in her fourth pregnancy, was admitted in labor a month from term, on June 7, 1941. The patient had had two classic cesarean sections in 1936 and 1939, respectively, because of a funnel pelvis. On the day before admission, the patient complained of intermittent pain in the lower part of the abdomen which continued and became severe. On admission the patient was in good condition. Labor pains occurred every few minutes, and a cystic mass became palpable in the lower part of the abdomen during each pain. There was tenderness over the abdominal scar. The fetal heart tones were good. Rupture of the uterus was diagnosed. At operation there was found a complete separation of the old scar. The membranes were intact and were bulging out of the uterus during the pains. The live baby was extracted and the old scar repaired. The patient made an uneventful recovery and was discharged fifteen days later.

#### RUPTURE OF THE UTERUS DUE TO TRAUMA

CASE 16.—L. C. L., aged 41, a quintipara in her sixth pregnancy, was admitted on Oct. 14, 1935. She had been in labor with ruptured membranes for fifteen hours. During this time, a midwife had tried to effect delivery by pushing on the fundus of the uterus. The previous deliveries had been uneventful. On admission, the patient was in desperate condition with a pulse rate of 140 and generalized abdominal tenderness. The fetal heart was not heard. During the preparations for craniotomy, a tear in the lower uterine segment was discovered. At operation, the fetus was found in the peritoneal cavity, and there was a tear through the lower uterine segment extending to the left lateral pelvic wall. Subtotal hysterectomy was done, and the patient died before supportive measures could take effect.

CASE 17.—C. L. F., aged 32, a tertipara, was admitted on March 13, 1937, two weeks past the expected date of confinement, because of high fever two days after delivery. The baby had been delivered stillborn with forceps; after this, the placenta had been manually removed. The previous deliveries had been uneventful. On admission, the patient was extremely sick and was treated for puerperal sepsis. Six days after admission, a cystic mass was felt in the abdomen. At operation, old blood was removed from the peritoneal cavity. A small rupture in the anterior wall of the uterus and a mass of matted bowel were not disturbed. The wound was drained, and patient recovered and was discharged twenty-three days after the operation.

CASE 18.—W. C. C., aged 36, a quintipara in her sixth pregnancy, was admitted at term on Nov. 21, 1937. A midwife had ruptured the membranes early in labor, the duration of which had been twenty-six hours. Eleven hours before admission, the midwife had tried to hasten delivery by pressure on the fundus of the uterus; during this procedure, the patient had a sudden sharp pain, and regular uterine contractions ceased. The previous deliveries were uneventful, and the pelvic measurements were normal. On admission, the patient was in shock; the abdomen was tense and tender, and the fetal parts were easily felt. The fetal heart tones were not heard. At operation, the fetus and the placenta were free in the abdominal cavity, and the rupture extended transversely across the lower uterine segment. Subtotal hysterectomy was done, and a blood transfusion was given during the operation. The postoperative course was relatively smooth, and the patient was sent home thirty days later.

CASE 19.—L. T. H., aged 39, a quartipara in her fifth pregnancy, was admitted on Nov. 21, 1938, two weeks before the expected date of confinement. Subtotal thyroidectomy had been done several years previously; after this tetany developed requiring calcium treatment. She also had chronic interstitial nephritis. The patient had been admitted at six months' gestation because of hypertension and retinal hemorrhage. Her condition improved, and she was allowed to go home. She was admitted in labor, which progressed satisfactorily for twelve hours; at the end of this time, the cervix was completely dilated, and the fetal head was seen at the vulva. Her general condition was good. A physician tried to assist delivery by pushing on the fundus of the uterus during a uterine contraction. The pains ceased, the fetal head receded, and the patient went into a state of collapse. A blood transfusion was given during the operation. The baby was dead in the peritoneal cavity, and the rupture extended obliquely through the right side of the lower uterine segment. Subtotal hysterectomy was done. The patient made a smooth recovery and was discharged on the twenty-fourth day after the operation.

#### RUPTURE OF THE PREGNANT HORN OF A BICORNUATE UTERUS

CASE 20.—C. C. F., aged 21, was referred to the Peiping Union Medical College Hospital in her first pregnancy on Dec. 29, 1936, near term. The patient was said to have been in labor for three days when labor ceased. After several days, the physician thought it best to induce labor by the introduction of a bougie and found that the uterus seemed to be empty. The condition of the patient was good, and rupture of the uterus was not suspected. On admission, the baby was superficially felt; the fetal heart was not heard, but there was no abdominal tenderness. At operation, the dead fetus was found in the abdominal cavity. The whole summit of the left horn of the bicornuate uterus had ruptured. The right horn was the size of a hen's egg. The enlarged left horn was removed, and the patient made an uneventful recovery.

#### RUPTURE OF THE UTERUS DUE TO UNKNOWN CAUSES

CASE 21.—L. S. Y., aged 29, a secundipara in her third pregnancy, was admitted at term on Nov. 1, 1935. During her nine hour labor, she had been examined by a midwife. The fetal head had been seen at the vulva but had now receded, and the patient had fainted. Her first two deliveries had been easy. On admission, the patient was in shock; the fetal heart was not heard, and there was much abdominal tenderness. By vaginal examination, the fetal arm and a tear in the anterior wall of the lower uterine segment could be felt. A blood transfusion was given, and at operation the fetus and the placenta were found free in the abdominal cavity. There was a complete rupture through the right lateral wall of the uterus. Subtotal hysterectomy was done, and after a stormy course she was sent home on the thirty-sixth day after the operation.

CASE 22.—L. P. M., aged 32, a sextipara in her seventh pregnancy, was admitted two days from term on Nov. 9, 1936, in labor for forty-eight hours and with ruptured membranes for twenty-four hours. The patient had been manipulated by a midwife. The previous deliveries had been spontaneous and easy. On admission, the patient was exhausted and dehydrated. The abdomen was tender, and the fetal parts were felt superficially. No fetal heart was heard. The pelvis was of the funnel type. On opening the abdomen, the fetus and the placenta were free in the abdominal cavity. The uterus was ruptured anteriorly through the left side to the left broad ligament and from the cervix into the vagina. Total hysterectomy was done.



Blood was given after the operation. The next day, the abdomen became much distended, and the patient had a chill and a high fever, followed by unconsciousness. She died forty-one hours after admission.

CASE 23.—L. J. S., aged 45, an undecimipara in her twelfth pregnancy, was admitted on Sept. 4, 1937, one week past term. She had been in labor for three days. The membranes were ruptured, and regular pains had ceased for seventeen hours. A midwife had made many examinations. Previous deliveries had been uneventful. On admission, the patient was in shock. There was moderate vaginal bleeding; no fetal heart tones were heard; the abdomen was tender, and the fetus was easily palpable. On vaginal examination, a tear in the anterior vaginal wall was found, but the fetus could not be reached. When the abdomen was opened, the fetus, the placenta and much old blood were found in the peritoneal cavity. Subtotal hysterectomy was done, and a blood transfusion was given. The patient died of peritonitis eleven hours after the operation. Hemolytic streptococci was demonstrated by a blood culture.

CASE 24.—C. T. S., aged 25, a primipara in her second pregnancy, was admitted at term on June 20, 1940, in labor complicated by dysentery. The pelvic measurements were normal, and there was a scar in the posterior vaginal wall, probably a result of the previous delivery. The fetal head failed to engage in the pelvic inlet, and after active labor of seventeen hours' duration and when the cervix was 8 cm. dilated, the fetal heart tones disappeared, and there was constant abdominal pain. The patient was operated on immediately, and the dead baby and the placenta were found in the peritoneal cavity. There was a large tear across the anterior surface of the lower uterine segment, extending into the left broad ligament. Subtotal hysterectomy was done, and a blood transfusion was given during the operation. Recovery was smooth.

#### RUPTURE OF THE UTERUS DURING LABOR DUE TO FETAL CAUSES

##### RUPTURE OF THE UTERUS DUE TO TRANSVERSE PRESENTATION OF THE FETUS

CASE 25.—L. Y. H., aged 25, a quintipara, was referred from another institution on Aug. 30, 1934, because of abdominal pain for one day following delivery. The fetus had presented transversely. After failure of an attempt at decapitation, the baby had been delivered by podalic version and extraction. The patient was sent to the Peiping Union Medical College Hospital in shock. There was generalized abdominal tenderness, and complete rupture of the uterus was found on vaginal examination. At operation, the tear was found to extend through the left broad ligament midway to the fundus. Subtotal hysterectomy was done, and a blood transfusion was given. She died twenty-four hours after admission. Autopsy showed general peritonitis, myometrial abscess and hemolytic streptococcic septicemia.

CASE 26.—L. T. L., aged 34, a duodecimipara in her thirteenth pregnancy, was admitted on May 7, 1935, two weeks past term. She had been in labor for thirty-two hours, and a fetal arm had been prolapsed for eight hours. There had been repeated attempts on the part of a midwife to effect delivery. The previous obstetric history was not significant. There was generalized abdominal tenderness, and a decapitation was done with difficulty. The abdomen became distended, and profuse bleeding, arterial in character, appeared on the fifth day post partum. A blood transfusion was given and the uterus packed, but the patient died. *Clostridium welchii* was obtained from the culture taken from the uterus.

CASE 27.—P. Y. C., aged 32, a quartipara in her fifth pregnancy, was admitted on March 25, 1936, after a labor of seven hours' duration. A fetal arm and the cord had been prolapsed for three hours, and attempts of a midwife to deliver the baby had been unsuccessful. The previous deliveries had been spontaneous. On admission, the patient was in shock; the pulse rate was 130 and poor in quality; the abdomen was tender, and the fetal heart tones were not heard. Delivery was effected by decapitation. After this, two tears in the cervix were found; the one on the right extended into the broad ligament. Repeated blood transfusions were of no avail, and the patient died four days later. A blood culture yielded a growth of hemolytic streptococci.

CASE 28.—C. C. C., aged 34, a tertipara in her fourth pregnancy, was admitted on June 21, 1937, two weeks past term. She had been in labor for six hours, and the membranes had been ruptured for three hours; this was followed by prolapse of a fetal arm. A midwife had tried to deliver the baby by pulling on the arm. The fetal heart tones were absent. Decapitation was done. A tear in the lower uterine segment was found through which part of the intestine was felt. The family refused to allow operation and took the patient home. A social worker has since reported that the patient is living and well.

CASE 29.—T. H. Y., aged 34, a tertipara in her fourth pregnancy, was admitted on Dec. 30, 1937, two weeks before term. She had been in labor for sixteen hours, and the fetal arm had been prolapsed for six hours. Previous deliveries had been uneventful. She had had severe abdominal pain on the day before admission and was examined by a neighbor. On admission, the patient was restless; the pulse was weak and poor in quality, and the temperature was 38.5 C. (101.3 F.). The abdomen was tender; the fetal heart was not heard, and the uterus remained in tetanic contraction. Decapitation was done; after this, a complete rupture of the uterus through the left broad ligament was discovered. On opening the abdomen, general peritonitis was evident. Subtotal hysterectomy was done, and the patient died three days later.

CASE 30.—L. C. M., aged 33, a sextipara in her seventh pregnancy, was admitted on Feb. 9, 1938, two weeks before term. Labor had been in progress for two days. The membranes had been ruptured for ten hours and a fetal arm prolapsed for eight hours. Regular pains had ceased; the patient had become pale and restless and had examined herself. On admission, the patient was in shock; the fetal heart was not heard; the fetus was superficially felt, and shifting dulness was demonstrable. There was a spurt of flatus as the abdomen was opened. Complete rupture through the left broad ligament was found, but the fetus was still in the uterus. Subtotal hysterectomy was done, and the patient died sixteen hours after admission. Two blood cultures were obtained and both showed beta hemolytic streptococci.

CASE 31.—H. S. K., aged 35, a septipara, was admitted on Dec. 27, 1939, one week past term, because of severe abdominal pain for two days after delivery. The baby had been in transverse presentation and was extracted by a physician. The placenta was also manually removed. After delivery, there was abdominal pain, fever, nausea and vomiting. On admission, the patient was unconscious; the temperature was 38.6 C. (101.4 F.), and the pulse rate was 150. There were generalized boardlike rigidity over the abdomen, petechia over the skin and signs of pneumonia. A blood transfusion was given, but the patient died five hours after admission.

*Shigella paradysenteriae* of the mannite-fermenting group was demonstrated in a blood culture. A postmortem pelvic examination revealed a tear in the lower uterine segment extending into the left broad ligament.

CASE 32.—L. F. S., aged 44, a nonipara, was admitted on Jan. 3, 1940. She had been in labor for three days and was repeatedly examined by a midwife. She had been admitted to another hospital, where decapitation was done because of the death of the baby and the prolapse of the fetal arm. It was then found that there was a rupture of the posterior wall of the uterus, and the patient was referred to this hospital. The diagnosis was confirmed, and with the patient in relatively good condition, subtotal hysterectomy was done. The rupture extended through the posterior and left wall of the cervix. The lower uterine segment and both the anterior and the posterior leaf of the left broad ligament were torn. A blood transfusion was given during and after the operation. Signs of peritonitis and bronchopneumonia soon appeared, and the patient died fifty hours later.

CASE 33.—F. H. M., aged 36, a septipara in her eighth pregnancy, was admitted on March 7, 1940, two weeks before the expected date of confinement. She had been in labor for seven hours, and a fetal arm had been prolapsed for four hours; this may have prompted repeated examinations by a midwife. On admission, the abdomen was tender, and the fetal parts were easily felt. Decapitation was done, and the placenta was manually removed. On examination, complete rupture through the left wall of the lower uterine segment and the left broad ligament was found. Subtotal hysterectomy was done and followed by a blood transfusion. The post-operative course was uneventful, and the patient left the hospital after twenty days.

#### RUPTURE OF THE UTERUS DUE TO COMPOUND PRESENTATION OF THE FETUS

CASE 34.—K. K. T., aged 35, an oetipara in her ninth pregnancy, was admitted on Oct. 30, 1937, three weeks after the expected date of confinement. She had been in labor with ruptured membranes for eight hours. There was slight contraction of the pelvis. On vaginal examination, it was found that both feet, the left hand and the head of the fetus presented at the pelvic inlet. Decapitation was done with difficulty, and thereafter an incomplete rupture in the anterior surface of the lower uterine segment was discovered. There were no external bleeding and no further interference. On the next day, the abdomen became distended, and the blood hemoglobin content dropped from 12.2 Gm. to 8.2 Gm. per hundred cubic centimeters. Blood transfusions were given, but the patient died.

CASE 35.—L. Y. Y., aged 31, a quintipara in her sixth pregnancy, was admitted on Nov. 30, 1938, four weeks before term. She had been in labor for twelve hours; the membranes had been ruptured for four hours, and she had been attended by a midwife. On admission, the patient was in a state of collapse, and there were no uterine contractions or fetal heart tones. On vaginal examination, the fetal head and arm were found presenting at the inlet, and there was a rupture extending through the lower uterine segment on the right side. An intravenous injection of dextrose solution was started, but the patient died ten minutes after admission.

#### RUPTURE OF THE UTERUS DUE TO EXCESSIVE SIZE OF THE BABY

CASE 36.—L. H. P., aged 32, a tertipara in her fourth pregnancy, was admitted on Jan. 23, 1938, one week past term. She had been in labor for sixty-six hours. During the last fourteen hours, the patient became short of breath; regular labor pains stopped, and the presenting part receded. On admission, the patient was in

a moribund state; the abdomen was tender; the fetal parts were easily felt, and no fetal heart tones were heard. When the abdomen was opened, the baby, which weighed 4,100 Gm., and the placenta were found in the peritoneal cavity. There was a rupture in the cervix extending into the anterior wall of the vagina. Total hysterectomy was done, and the patient died three hours after admission.

CASE 37.—C. C. J., aged 31, a tertipara in her sixth pregnancy, was admitted on July 24, 1937, twenty-six days after the expected date of confinement. She had been attended by a midwife during her labor of seventeen hours. The pelvic measurements were normal, and her previous deliveries had been uneventful. The patient was in good condition when admitted, and the cervix was completely dilated. The dead baby in breech presentation was extracted and was found to weigh 4,300 Gm. A rupture in the anterior surface of the lower uterine segment was found. At operation, the 12 cm. long transverse rupture was found completely to separate the bladder from the lower uterine segment. A blood transfusion was given, and subtotal hysterectomy was done. Five days after the operation, a vesicovaginal fistula was evident; this was repaired one month later. The patient was discharged twenty-six days after repair of the fistula.

CASE 38.—T. T. M., aged 21, a primipara in her second pregnancy, was admitted at term on Nov. 21, 1940, in a moribund condition. She had been in labor for seventeen hours, and the fetal arm had been prolapsed for eleven hours. Repeated manipulations by a midwife had caused much bleeding. The previous delivery had been uneventful. On admission, the patient was in a desperate condition. The abdomen was tender, and the fetal parts could be superficially felt. At operation, the peritoneal cavity was filled with old blood, the fetus and the placenta. The baby was dead and weighed 4,200 Gm. A complete rupture extended on the left from the cervix to the cornu. A blood transfusion was given, and subtotal hysterectomy was done. In spite of supportive measures, the patient died on the sixth day after operation. Autopsy demonstrated retroperitoneal abscess and general peritonitis.

#### RUPTURE OF THE UTERUS DUE TO HYDROCEPHALUS

CASE 39.—Y. J. C., aged 30, a sextipara in her seventh pregnancy, was admitted on Dec. 30, 1938, two weeks after the expected date of confinement. She had been in labor with ruptured membranes for eighteen hours; this resulted in delivery of the breech and body up to the shoulder girdle. A midwife had attended the case. On admission, the patient was in shock; the abdomen was tender and much distended, with shifting dullness, and the uterus was deviated to the right in a state of constant contraction. The presence of meningocele and hydrocephalus in the baby was clear, and delivery was readily effected by craniotomy. Examination thereafter showed complete rupture of the anterior wall of the lower uterine segment which extended into the left broad ligament. The patient promptly died.

CASE 40.—T. S. C., aged 23, a secundipara in her third pregnancy, was admitted on June 20, 1939, at term. She had been attended in her three day labor by a midwife. Regular labor pains had ceased sixteen hours prior to delivery. On admission, the patient was in coma; the temperature was 39.5 C. (103.1 F.), and the pulse rate was 160. The fetal heart could not be heard. A blood transfusion was given before the operation. At operation there was much free blood in the peritoneal cavity. The cervix and the uterus were completely torn through on the left side. The hydrocephalic fetus was still in utero. After extraction of the baby, subtotal hysterectomy was done. The patient died twelve hours after admission.

CASE 41.—C. T., aged 36, a sextipara in her seventh pregnancy, was admitted on Sept. 29, 1939, two weeks after the expected date of confinement. She was referred from another hospital after a labor of forty-four hours. Her pelvic measurements were normal, and all the previous deliveries had been uneventful. On admission, the patient was in shock; the fetal heart could not be heard, and the fetal parts were readily palpable. When the abdomen was opened, the fetus with hydrocephalus and meningocele was in brow presentation. A rupture of the anterior surface of the lower uterine segment extended into the fundus on both the right and the left side. Subtotal hysterectomy was done. A blood transfusion was given during the operation, and others were given repeatedly thereafter. A pelvic abscess developed; this was drained through the cervical stump. After a stormy course, the patient was discharged fifty days after the operation.

#### RUPTURE OF THE UTERUS DUE TO TUMOR OF THE FETUS

CASE 42.—C. P. H., aged 24, a secundipara in her third pregnancy, was admitted on Feb. 5, 1939, three weeks before the expected date of confinement. She had been in labor for sixteen hours, and the breech had protruded from the vulva for four hours. Attempts of a midwife to deliver the baby by traction had failed. A large tumor the size of a man's head over the sacral region of the baby was found to be the cause of the dystocia, and embryotomy was performed. Examination after delivery showed a tear into the left broad ligament. The abdomen became distended, and the patient ran a stormy course. On the twelfth postpartum day, the patient was reexamined, and a complete tear through the left broad ligament was found. The family insisted on taking the patient home, and attempts to follow up the case were unsuccessful. The tumor of the fetus proved to be teratoma.

#### RUPTURE OF THE UTERUS DUE TO THE PERSISTENT OCCIPITOPOSTERIOR POSITION OF THE FETAL HEAD

CASE 43.—C. C. T., aged 31, a quartipara in her fifth pregnancy, was admitted on June 26, 1940, and was said to be five weeks past term. She had been in labor for nineteen hours. A physician and a midwife had examined the patient and referred her to the Peiping Union Medical College Hospital. On admission, the fetal heart could not be heard, and the head presented deeply in the pelvis in left occipitoposterior position. The delivery was effected by means of craniotomy, cleidotomy and extraction. Vaginal examination then revealed rupture of the uterus. At operation, a tear was found in the anterior wall of the lower uterine segment under the bladder. This was repaired, and subtotal hysterectomy was done. Blood transfusions were given after operation and repeatedly during her stormy convalescence. The abdominal wound became infected, and secondary closure was necessary. The patient recovered and was discharged on the forty-fourth postoperative day.

#### RUPTURE OF THE UTERUS DURING PREGNANCY

CASE 44.—M. H. T., aged 39, a sextipara in her seventh pregnancy, was admitted on Nov. 12, 1938, at six months' gestation, because of sudden pain in the lower part of the abdomen accompanied by a fainting spell. She had been hospitalized in early pregnancy for hyperemesis. All previous deliveries had been uneventful. On admission, the patient was in a state of collapse. There was generalized abdominal tenderness and rigidity. The fetal heart was not heard, and there was no external bleeding. A transfusion of 500 cc. of blood was given before operation. On opening the abdomen, 3,000 cc. of dark blood was removed. The bleeding came

from a partial rupture of the posterior wall of the uterus near the right cornu. The dead fetus was removed by hysterotomy, and subtotal hysterectomy was done. Blood transfusions were given during the operation and repeatedly thereafter. The patient seemed on the way to recovery when symptoms suggesting thrombosis of the pelvic veins appeared. She died twenty-two days after the operation. The partial rupture was 4 cm. in length, extended 1 cm. into the myometrium and was caused by a ruptured varix.

## DISTRIBUTION

Two of these patients were 19 years old, and the oldest was 43. Only 2 of the 44 patients were in their first pregnancy; this emphasizes the overwhelming incidence in multiparas. In 38 cases there were complete ruptures of the uterus, while in 6, the ruptures were incomplete. This

TABLE 1.—*Sites and Types of Rupture of the Uterus.*

Site	Type	
	Complete	Incomplete
Lower segment		
Transverse .....	13 (Cervix involved in 1)	
Left .....	11 (Cervix involved in 2)	3
Right .....	8 (Cervix involved in 4)	
Bilateral .....		2
Fundus		
Posterior wall .....		1
Anterior wall .....	2	
Bicornuate uterus .....	1	
Cesarean section scar .....	3	
Total .....	33	6

predominance of complete ruptures agrees with the findings of most authors on this subject, but we believe that incomplete rupture is much more common than is generally suspected. There must be many instances of postpartum bleeding caused by partial rupture in which the uterus is packed and the patient recovers without the cause of the bleeding being established.

As to location, in the group of complete ruptures, 11 were through the left lateral wall of the uterus; 8, through the right lateral wall; 13, transversely through the anterior wall; 3, through an old classic cesarean section scar, and 3, through the fundus. One of the last mentioned was through the horn of a bicornuate uterus (case 20). In the group of partial ruptures, 5 occurred in the lower uterine segment and 1 in the fundus. Of the ruptures in the lower uterine segment, 3 were found on the left side, and 2 were bilateral. Only 1 occurred during pregnancy, while 43 were associated with labor. Of the latter, 24 were judged to be due to maternal causes and 19 to be of fetal origin (table 1).

## CAUSATION

Because so often many unknown factors were concerned, it is impossible accurately to classify these cases, but they have been grouped as to what seems to us to have been the primary etiologic factor. At this point, a few words concerning osteomalacia may be opportune. Osteomalacia is a progressive deficiency disease. Insufficient utilizable calcium and phosphorus in the diet with too little vitamin D together with a drain of these minerals such as occurs during lactation, may produce the condition. The common symptoms are aches and pains in the muscles and the bones of the thighs and the back. With sufficient decalcification, deformities of bone, especially of the pelvis and the spinal column, occur due to pressure. Pelvic deformity is characterized chiefly by varying degrees of collapse of the pelvis, marked shortening of the oblique diameters of the pelvic inlet and contraction of the transverse diameter of the outlet. In America, one seldom, if ever, sees deformity of the pelvis to such a marked extent.

With regard to the ruptures of the uterus thought to be due to maternal causes, in the first group caused by contraction of the pelvis, 9 out of 12 cases were due to osteomalacia. Two of the remaining 3 patients of this group, 1 of whom was a chondrodystrophic dwarf, had a generally contracted pelvis, and 1 had a simple flat pelvis. The efforts of a midwife to deliver the baby through insufficient space may have accounted for some of these ruptures. The remaining patients in this study all had pelvic measurements within the accepted limits of normal.

Rupture of the uterus through cesarean section scar occurred in 3 of these patients, 2 of whom had had infection of the abdominal incision after the previous operation. It is probable that these uterine scars were thin or poorly healed. Also, if the placental site is beneath the scar, the invasion of the chorion tends to weaken the wall of the uterus at this point, as emphasized by Holland.<sup>3</sup> The placental site was found beneath the scar in 3 of the 6 patients with rupture of a cesarean section scar observed in the Peiping Union Medical College Hospital, and this cause of rupture could be included as one of the intrinsic type mentioned by Seley.<sup>4</sup>

Trauma is known to have produced rupture of the uterus in 4 cases. The fumbling efforts of an untrained midwife to hasten delivery by pushing on the fundus of the uterus were responsible for the damage done in cases 16 and 18. The rupture in case 19 occurred in our own delivery room. We consider pushing on the uterine fundus instead of using forceps, where indicated, to be obsolete obstetrics even though it is still practiced by some. Kristeller's expression is no longer done in

3. Holland, E.: *Proc. Roy. Soc. Med. (Sect. Obst. & Gynaec.)* **14**:22, 1921.

4. Seley, A. D.: *Am. J. Obst. & Gynec.* **33**:857, 1937.

this hospital. Considering the history, the location and the type of rupture, it is probable that in case 17, the uterus was perforated during manual removal of the placenta.

Rupture through the pregnant horn of a bicornuate uterus at term is illustrated by case 20. An intrinsic cause, such as weakening of the wall of the uterine fundus associated with the congenital anomaly, is possible.

Four cases are included in our group of cases of rupture due to unknown causes. In 3 cases, the pelvic measurements were normal, and in 1, the mild degree of contraction of the transverse diameter of the pelvic outlet was probably not the cause of the rupture. All the babies were of normal weight. The ruptures in cases 21, 22 and 23 may have

TABLE 2.—*Classification of Cases According to Cause of Rupture of the Uterus.*

Cause	Cases	Outcome	
		Lived	Died
Rupture during labor due to a maternal cause:			
Contracted pelvis .....	12	4	8
Cesarean section scar.....	3	3	..
Trauma .....	4	3	1
Bicornuate uterus .....	1	1	..
Unknown cause .....	4	2	2
Rupture during labor due to a fetal cause:			
Transverse presentation .....	9	2	7
Compound presentation .....	2	..	2
Excessive size .....	3	1	2
Hydrocephalus .....	3	1	2
Tumor of the fetus.....	1	Unknown	..
Persistent occipitoposterior position .....	1	1	..
Rupture during pregnancy.....	1	..	1
Total .....	44	18	25

been due to the manipulations of the midwife in attendance, while in case 24, cervical dystocia or malposition of the fetal head may have caused the accident.

Turning to the baby as a probable cause of rupture of the uterus, one finds that there were 11 cases of transverse or shoulder presentation of the fetus. In 1 case, rupture was associated with a generally contracted pelvis (case 6), and in another, the baby was excessively large (case 38). These 2 cases are included in their proper groups. In 2 cases (cases 25 and 31), the rupture was probably caused by version and extraction before the patients were admitted here. The remaining 9 patients arrived at the hospital with neglected transverse presentation of the fetus. We have grouped them together under this heading, for it is impossible to estimate how much damage had been done by midwives trying to terminate labor by pulling on the fetal arm. It is possible also that our own careful efforts at decapitation may have in some instances completed the damage which was already started.



There were 2 instances of rupture due to compound presentation of the fetus; these were tragedies similar to some of those of the previous group. In case 34, decapitation may have contributed to the injury while patient 35 died within a few minutes after admission.

According to Lee,<sup>5</sup> in his review of 1,400 Chinese babies, the average weight is 3,000 Gm. We may consider that babies of more than 4,000 Gm. are definitely overweight. Since all 3 of our patients whose babies were listed as overweight had normal pelves, it is fair to assume that these ruptures of the uterus were caused by the excessive size of the baby.

In 3 cases, delivery was impossible because of hydrocephalus of the fetus. In case 39, it is probable that the rupture was caused by the traction with which the midwife tried to terminate the labor. Cases 40 and 41 were examples of injury to the patient because the attendant failed to recognize the condition.

The rare teratoma of the sacrum of the fetus was clearly the cause of the rupture of the uterus in case 42.

Persistent occipitoposterior position of the fetal head was responsible for only 1 of these accidents. The patient had had prolonged dry labor resulting in impaction of the fetal head. The signs and symptoms of rupture of the uterus were present on admission to the hospital, and it is not probable that a destructive operation on the fetus was the cause of the rupture.

Finally, there was only 1 case in which rupture was not associated with labor. This patient was in the sixth month of her pregnancy and had the typical symptoms of concealed hemorrhage. There had been no previous pelvic or abdominal operation, and the cause of rupture was established as a ruptured varix.

#### MORTALITY RATE AND PROGNOSIS

Eighteen of the 44 mothers lived; 25 died, and the outcome of 1 is unknown since she was discharged against the advice of the attending staff. Only 3 babies lived. In viewing this record one must consider the desperate condition of most of these patients when they arrived at the hospital. The length of labor is important because it influences the prognosis. Among those mothers who recovered, the average length of labor was seventeen hours compared with an average of thirty-eight hours for those who died. The time elapsing between rupture and treatment is also important. For those who recovered there was an average of six hours between the occurrence of the rupture and the treatment compared with an average of seventeen hours for those who

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5. Lee, S. W.: *Nat. M. J. China* 14:707, 1930.

died. The most frequent immediate causes of death were peritonitis, bronchopneumonia, bacteremia and paralytic ileus. It is surprising indeed that in 44 accidents attended by trauma to tissues and infection, thrombosis of the pelvic veins was suspected to have occurred only once. Phlebitis and thrombosis, however, are rare among the Chinese.

The widespread increase in the frequency of cesarean section makes the group of rupture of a cesarean section scar of especial importance. All 3 of the patients in this group recovered, and 2 of the babies lived. In a previous report from this department, Wang<sup>2</sup> described 3 cases of rupture of a previous cesarean section scar. Two of the patients lived, and 1 died of intestinal obstruction treated by enterostomy. All 3 babies died. The classic type of cesarean section had been done on all 6 of the patients with rupture of a cesarean section scar seen in this department. The conclusion from our experiences that in cases of rupture of a cesarean section scar, the mortality rate for mothers and babies is considerably less than in cases of other types of spontaneous rupture agrees with that of many authors on this subject. Rupture of the uterus is a gradual or sudden separation attended by much less bleeding, and the baby has more of an opportunity to act as a tampon in the uterine tear. Further, the patients who have had a previous cesarean section are on the lookout for trouble since they have been told, or should have been, that the next delivery should take place in a hospital. In the past year and a half, we have had 8 cases of rupture of the uterus, 7 of which were complete, with the loss of 2 mothers. Seven different members of the staff did these operations following rupture of the uterus. Subtotal hysterectomy was carried out on 7 patients, and on 1 occasion the tear was simply repaired. In all operations requiring removal of the uterus, the same general technic was used, and it seems to have been of value.

#### SIGNS AND SYMPTOMS OF THREATENED RUPTURE

During pregnancy there may be no premonitory signs of rupture. As long as the membranes are intact there is not much danger of this accident. An exception was case 44. Ruptures of the uterus with the membranes intact have been observed, but these are rare and are usually due to changes in the uterine wall rather than to retraction. When the membranes have ruptured and all fluid has been lost and good uterine contractions are present with no progress in labor, especially if the patient is a multipara, one should make a careful examination with a view of making an early diagnosis of the cause of dystocia. The uterus may be pulled farther and farther over the head or the body of the child, and the elastic cervix and lower uterine segment may be abnormally

stretched. The vaginal portion becomes clamped between the head and the pelvic inlet, and if this mechanism continues, rupture occurs. The signs of overstretching of the uterus in the presence of strong uterine contractions may be summarized as follows: (1) pain and tenderness over the lower part of the abdomen, with or without strong uterine contractions; (2) edema and change of color of that portion of the cervix which is clamped between the head and the pelvis; (3) a groove between the symphysis and the umbilicus or higher indicating the contraction ring; (4) tension of the round ligaments; (5) increase in the pulse rate.

#### TREATMENT OF THREATENED RUPTURE

The best treatment is, of course, prophylactic. Women who have had a previous cesarean section should be within easy reach of adequate surgical help during pregnancy and labor. The site of a previous cesarean section scar must be repeatedly examined during labor to detect excessive thinning or tenderness. One must not forget that in the patient who has undergone a previous classic cesarean section, one or more spontaneous deliveries thereafter weaken the uterus and predispose it to rupture rather than prove that the scar is strong. Separation of such a scar occurring late in pregnancy or in labor indicates the need for prompt surgical intervention. When, after a previous cesarean section, there has been infection and long convalescence, elective cesarean section should be considered. More rigid indications for the first cesarean section and less rigid indications for the second and common adoption of the low segment operation would considerably reduce the incidence of rupture of the uterus from this cause. If pituitary extract is used at all before delivery, not more than 3 minims (0.18 cc.) should be given at one time, and if the uterus reacts violently to such medication, small amounts of ether should be given to control the uterus until the effect of the drug is gone. The pituitary extract, however, was not a cause of rupture in this series. With the development of signs and symptoms of threatened rupture, immediate delivery is mandatory. Delivery with forceps may be contraindicated in these cases, and version and extraction are always contraindicated.

If the baby is dead, the problem in delivery from below is to reduce its size. Craniotomy and decapitation are the most useful procedures, depending on existing conditions. If the baby is living and the probabilities of infection are not too great, low cervical cesarean section gives the best prognosis for mother and child. If the baby is living and the uterus obviously infected, cesarean section followed by supravaginal amputation should be done.

## SYMPTOMS AND SIGNS OF RUPTURE

At the time of rupture and thereafter, the signs and symptoms are definite. They vary somewhat according to whether the rupture is complete or incomplete. They may be summarized as follows:

1. Sudden sharp pain, followed by the symptoms of shock, is present (33 cases).

2. There is gradual cessation of uterine contractions, which may indicate incomplete rupture (5 cases), or sudden cessation of strong contractions, which indicates complete rupture (21 cases).

3. There are changes in the contour of the abdomen. The baby may be more easily palpable (19 cases), and a tumor mass representing the uterus may be felt in either lower quadrant of the abdomen.

4. Bleeding depends on the extent of the tear. When the signs of hemorrhage are out of proportion to the amount of visible bleeding, one should think of concealed hemorrhage. Acute anemia gradually develops. Thirteen of our patients had acute anemia, but many were so dehydrated with consequent concentration of hemoglobin that the actual number of cases of anemia is not known.

5. A slowly growing tumor alongside of the uterus, with developing emphysema and bleeding, is indicative of incomplete rupture (case 12).

6. Recession of the presenting part before delivery may occur (3 cases). Retention of the placenta after delivery has been seen occasionally.

## TREATMENT AFTER RUPTURE

After every difficult delivery, especially when associated with manipulation or instrumentation, the physician should explore the uterus and the lower part of the genital tract. If incomplete rupture is found, repair from below and packing can frequently be carried out. Even when the rupture is complete, one may be forced to rely on packing as the only available method of treatment. Two cases of this sort were reported by Maxwell<sup>6</sup>; both patients lived. According to Freund,<sup>7</sup> the mortality rate after packing of the uterus in instances of complete rupture is about twice as great as when treatment by supravaginal amputation of the uterus has been carried out. However, even in a case of incomplete rupture of the uterus, if a hematoma is already present alongside of the uterus, abdominal operation should be carried out when the patient is in a condition to withstand the procedure. If complete rupture is found, one should prepare to give a transfusion, and while waiting for blood, one should give adequate dextrose, usually from 500 to 700 cc.

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6. Maxwell, J. P.: *China M. J.* 24:341, 1910.

7. Freund, R., in Halban, J., and Seitz, L.: *Biologie und Pathologie des Weibes*, Berlin, Urban & Schwarzenberg, 1927, vol. 8, pt. 1, p. 863.

of a 20 per cent solution; this should be given slowly after testing the urine for sugar. The infusion requires about one hour. The dextrose infusion should be replaced by blood as soon as this is available. When the child is free in the abdominal cavity, attempts to deliver it through the tear are absolutely contraindicated; this was emphasized by De Lee,<sup>8</sup> but the procedure is still, unfortunately, occasionally done.

Packing from below is sometimes useful to control bleeding while preparations for operation are in progress. Sometimes rupture at the site of a previous cesarean section scar can be treated by excision of the scar and repair, but in other cases, when the tear is uneven, removal of the uterus by supravaginal hysterectomy is the treatment of choice, because such a procedure controls the bleeding and removes the focus of infection. Most patients are in such a critical condition that a prolonged operation is undesirable.

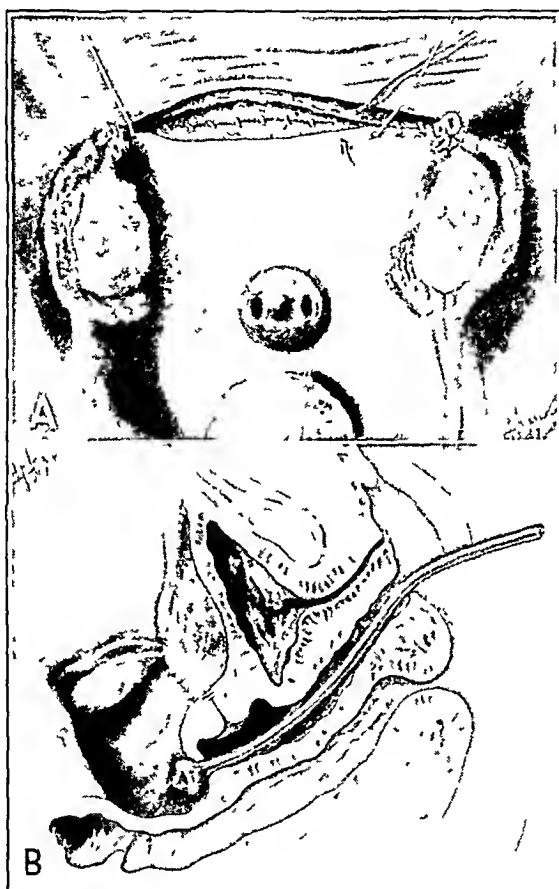
Our results have considerably improved with the adoption of a simple technic. In some instances, the cervix was found to be torn, and the rupture extended up through one broad ligament. Removal of the cervix is not urgent, and we usually prefer not to extend the operation by removing it. We believe that as nearly uniform a technic as possible is the answer to the problem as regards the surgical treatment of this condition in any hospital. The technic must not be complicated, so that any one familiar with abdominal operations can do it. The surgical procedure at this hospital is a modification and a combination of the technic observed in several hospitals and may be briefly described as follows:

The position of the patient on the operating table is important in order that the operator can do his best work. We have removed the foot or lower one third of the table for all gynecologic laparotomies. The patient's thighs are placed in leg holders on the same level as the abdomen; the knees are widely separated, and the buttocks protrude slightly beyond the edge of the table, while the legs simply hang at the knees. The operator and his first assistant are alone on each side of the table and are not encumbered by the presence of too many persons in close quarters. The second assistant stands between the patient's thighs and close-up in the field. After the abdomen is opened and the fetus and the placenta are removed, the bladder fold of the peritoneum is first transversely incised and pushed downward with the bladder. This transverse incision is continued into the tear in the damaged broad ligament. If a hematoma is present, it can be quickly evacuated and the bleeding points controlled. The second assistant is in position to help identify disturbed anatomic relations. With the gloved hand, from

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8. De Lee, J. B.: *Principles and Practice of Obstetrics*, ed. 7, Philadelphia, W. B. Saunders Company, 1938, p. 860.

below if necessary, he can readily identify the torn cervix and the vaginal vault for the operator. By the use of through and through sutures, the rent in the cervix can be quickly and safely repaired, and the uterus may then be amputated as in any supravaginal hysterectomy. A continuous suture is placed in the remaining cervical portion (*A* in the illustration), which begins laterally at one angle and includes the mucosa and about one half of the thickness of the musculature across the cervix



In *A* is shown how, after supravaginal amputation of the uterus, the remaining cervical portion is closed with a continuous suture in two layers. This is simple and prevents oozing. In *B* is shown how, after closure of the cervix, insertion of a large mushroom catheter through the posterior vaginal vault into the cul-de-sac provides easy, quick and efficient drainage

to the opposite angle. The same suture may be continued back to its original point, including the remaining muscle wall and serosal surface. Oozing is thereby prevented. The ligamentous attachments of the uterus are loosely anchored to the angles of the cervix with the same continuous suture, and the bladder fold of peritoneum is used to cover the raw surface. Drainage through the cul-de-sac by means of a

large mushroom catheter is easily provided (*B* in the illustration). The second assistant is in position to place an open clamp in the posterior vaginal vault beneath the posterior lip of the cervix, and the cul-de-sac is incised from above in order to place a drainage tube into the vagina. We believe that such a procedure provides better drainage than through the cervix or the abdominal wall. Ruptures which do not involve the cervix and its attachments are simpler to handle. The prevention and the treatment of ileus in the early postoperative period by decompression of the gastrointestinal tract by means of continuous suction have been of great value to these frankly infected patients. During this procedure, it is important to provide adequate amounts of physiologic solution of sodium chloride and dextrose solution, usually by the intravenous drip method. Uniformity in procedure is essential in any hospital if good results are to be obtained. The adoption of this technic, the liberal use of blood transfusions and parenteral fluids, the prevention of distention of the stomach and the upper part of the bowel by the application of continuous suction and the judicious use of chemotherapy have materially improved our results. After the initial blood transfusion subsequent transfusions are usually necessary, depending on the degree of anemia of the patient.

#### SUMMARY

The details about 44 patients with rupture of the uterus treated in the Peiping Union Medical College Hospital during the past seven years have been reviewed. Year by year there has been a definite decrease in the mortality rate. The reasons for this decrease are: (1) improvement in the availability of blood for transfusion; (2) the adoption of a uniform technic in the surgical treatment; (3) the use of sulfanilamide and its derivatives; (4) the decompression of the gastrointestinal tract by the use of continuous suction.

In the treatment of acute anemia nothing takes the place of blood, and the convenience of using stored blood is of obvious importance. Improvements in chemotherapy have been a decided help to our patients and have no doubt prevented deaths in the late postoperative period, since most of those who died succumbed soon after operation and before the drug had had an opportunity to take effect. Although modifications must be made to meet the problems of individual cases, we believe that it is worth while to note the advantages of uniformity in the surgical procedure. We have therefore described the method in use at this hospital. It is true that the incidence of rupture of the uterus indicates the character of obstetric practice in any community, and further reduction in the present mortality rate must depend on better obstetric practice. This will come when the public understands the dangers of childbirth and when training programs for midwives and physicians gradually take effect.

# TREATMENT OF BURNS OF THERMAL ORIGIN

HARRY C. HULL, M.D.

BALTIMORE

During the past three years the literature on the treatment of burns has been prolific. Most of the articles have dealt with some one phase of the subject. Blood studies in shock due to burns and the correction of blood imbalance have come in for particular emphasis.

This communication is intended to be more comprehensive. It stresses again the improvement in the mortality rate due to the use of plasma in the treatment of shock accompanying severe burns. In addition, it undertakes to discuss other important factors concerned in the clinical management from the time of the accident to eventual cure or death. The article comprises two comparative series, one of 188 cases encountered from 1930 to 1939, the other of 92 cases occurring from March 1939 to November 1941. The reason underlying the comparison is that the latter series has been under the uniform management of a burn service in contradistinction to an unregulated regimen in the previous decade.

To facilitate the discussion, the factors concerned may be listed chronologically under the following heads: (1) the treatment of shock; (2) local cleansing of the burned area; (3) treatment of the burned area with various agents; (4) the removal of the eschar (if escharotic agents are used) and epithelization with or without graft; (5) complications; (6) prevention of contractures and follow-up with or without plastic reconstruction.

## SHOCK

"The period of shock in a burned patient is an entity itself and should be treated as such."<sup>1</sup> "We should fix attention upon the measures which affect the survival of the patient, regardless of their influence upon infection or epidermal growth."<sup>2</sup>

Despite these warnings, physicians when first called and interns in receiving wards are still at times so taken with the pitiful state of the patient that their attention is directed to the treatment of the burned

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From the Department of Surgery, University Hospital.

1. Aldrich, R. H.: Role of Infection in Burns, *New England J. Med.* **208**: 299-309, 1933.

2. Glover, D. M.: A Critical Evaluation of the Treatment of Burns, *Ann. Surg.* **113**:1090-1091, 1941.



area instead of to the treatment of shock. By this error, valuable time is lost, and this is responsible for death, especially of infants and young children.

For a severe burn seen by a physician at the patient's home the treatment is clear. The patient should be wrapped in sheets, blankets or any available covering, receive an injection of morphine and be removed as quickly as possible to an institution, where adequate shock treatment can be given. The treatment of the burned area is of secondary importance until shock has been treated and the patient is responding. This response may not be evident for several hours; during this period the lesions remain covered.

Much valuable contributory work has been done since 1920 and especially since 1930 to illustrate the conception of shock due to burns. Among the outstanding contributors have been Underhill,<sup>3</sup> Davidson,<sup>4</sup> Blalock,<sup>5</sup> Scudder,<sup>6</sup> Moon,<sup>7</sup> Elkinton,<sup>8</sup> Harkins,<sup>9</sup> Dunphy,<sup>10</sup> Freeman,<sup>11</sup> Davis<sup>12</sup> and many others, whose voluminous work cannot be reviewed in this article.

There are still controversial points as to the mechanism of the production of shock. There is, however, abundant experimental and clinical evidence to show that after a severe burn there is altered capillary permeability at the site of the burn with a leakage of the fluid portion of the blood at the site. In addition to the external loss there is also a greater accumulation of fluid in the tissues.<sup>6</sup> This loss of fluid results

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3. Underhill, F. P.; Kapsinow, R., and Fish, M. E.: Studies on Mechanism of Water Exchange Induced by Superficial Burns, *Am. J. Physiol.* **95**:315-339, 1930.

4. Davidson, E. C.: Tannic Acid in the Treatment of Burns, *Surg., Gynec. & Obst.* **41**:202-221, 1925.

5. Blalock, A., and Mason, M. F.: Blood and Blood Substitutes in the Treatment and Prevention of Shock, with Particular Reference to Their Use in War-time, *Ann. Surg.* **113**:657-671, 1941.

6. Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

7. Moon, V. H.: Shock: Its Mechanism and Pathology, *Arch. Path.* **24**: 642-663 (Nov.); 794-810 (Dec.) 1937.

8. Elkinton, J. R.; Wolff, W. A., and Lee, W. A.: Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns, *Ann. Surg.* **112**:150-156, 1940.

9. Harkins, H. N.: Experimental Burns: I. The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns, *Arch. Surg.* **31**:71-85 (July) 1935.

10. Dunphy, J. E.: Observation of the Pathology of Experimental Traumatic Shock, *Surg., Gynec. & Obst.* **72**:823-833, 1941.

11. Freeman, N. E.: The Mechanism and Management of Surgical Shock, *Pennsylvania M. J.* **42**:1449-1452, 1939.

12. Davis, H. A.: The Pathology of Shock in Man, *Arch. Surg.* **41**:123-146 (July) 1940.

in decrease of blood volume, blood flow (cardiac output) and plasma protein with accompanying hemoconcentration. These alterations can be well illustrated by various blood studies which constitute the basis for the use of intravenous plasma. Elkinton estimated that this shift or leakage continues until the fortieth hour after trauma, but in some of the cases in this series, blood balance was not obtained for fifty to sixty hours.

Recently Rhoads<sup>13</sup> reported that supplementing plasma with extract of adrenal cortex reduces the leakage period to as low as eighteen hours after shock. He warned that sodium chloride should be given only as indicated by blood estimations, as extract of adrenal cortex causes marked chloride retention.

*Management of Shock.*—In the clinical management of shock, it is the practice to obtain a basal line blood chemistry as quickly as possible after the usual shock measures have been instituted. Blood for this purpose is taken at the time plasma is first given (usually 500 to 1,000 cc. for adults, less for children). In hospitals in which blood banks are operating, this treatment can be started twenty to thirty minutes after the arrival of the patient. Requisitions on the first blood sample are made for hematocrit, red blood cell, hemoglobin and plasma protein determinations which are repeated at six hour intervals. These determinations are used as indexes for the amounts and the frequency of later plasma administration. Determinations of carbon dioxide, nonprotein nitrogen and chlorides are made on later blood samples. The giving of small amounts (300 to 500 cc.) of plasma every four to six hours, depending on the severity of shock as indicated by the hematocrit and protein studies, is advised. Recently, Harkins<sup>14</sup> reported a simple way to estimate the dose of plasma needed. "The amount of plasma needed can be roughly calculated for an average-sized adult as being 100 cc. plasma for every point the hematocrit exceeds the normal of 45, as long as the plasma proteins are above 6.0 Gm. per hundred cubic centimeters. When the plasma proteins are below 6.0 Gm. per hundred cubic centimeters, an additional 25 per cent of the calculated amount of plasma should be added for every gram the protein is below 6.0." An attempt is made to keep the protein at 6 mg. per hundred cubic centimeters and the hematocrit at 50 to 55 during the period of leakage.

At this institution, each unit (500 cc.) of plasma may be defined as the fluid portion obtained from 500 cc. of whole citrated blood, which is diluted to 1 pint with physiologic solution of sodium chloride.

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13. Rhoads, J. E.; Wolff, W. A., and Lee, W. A.: The Use of Adrenal Cortical Extract in the Treatment of Traumatic Shock of Burns, *Ann. Surg.* **113**:955-965, 1941.

14. Harkins, H. N.: Personal communication to the author.

Intravenous dextrose and sodium chloride are contraindicated during this period of shock since they will increase the tissue edema already present. Crystalloid solutions are rapidly lost from the circulation in a shocked patient and actually wash plasma protein out of the blood stream.<sup>15</sup> Plasma given frequently in indicated amounts is the answer to correcting protein loss until the period of leakage has stopped. In burns involving 30 to 40 per cent of the body area, the total amount of plasma necessary is approximately 4,000 cc. in the average adult. Then, any remaining protein deficiency can be readily corrected by using whole blood.

The handling of such a patient necessitates a hospital with an operating blood bank, day and night laboratory facilities and constant attention from the house and visiting staffs. By constant care in the first several days of the shock period, lives can be spared.

It is not intended to convey the impression that every patient shocked from burns can be saved by the present improved methods. At a certain level shock becomes an irreversible process. It is, however, to be emphasized that treatment of shock in cases of severe burns is of the greatest importance. It is not common sense in the light of present knowledge to spend the first valuable hours in cleaning and treating burned areas with local agents, only to lose the patient from shock. The importance of constant vigilance to this ever present complication of severe burns cannot be too often reiterated. Especially is this so in the case of children who are so labile in this regard and who, according to McClure,<sup>16</sup> make up 45 per cent of the 8,000 persons with lethal burns per year in this country.

#### LOCAL CLEANSING OF THE BURNED AREA

After the work and teachings of Davidson,<sup>4</sup> McClure,<sup>16</sup> Mason,<sup>17</sup> Aldrich<sup>18</sup> and others there should be no controversy about cleaning a burned area.

A burn should be considered as an open contaminated wound consisting for the most part of dead or damaged tissue. There should be no more hesitancy about cleaning a burned area than about cleaning a

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15. Harkins, H. N.: The Treatment of Burns, Brochure Prepared in Connection with Exhibit on Burn Shock, Scientific Exhibit, Section on Surgery, Ninety-Second Annual Session of the American Medical Association, Cleveland, June 2-6, 1941. Blalock and Mason.<sup>5</sup>

16. McClure, R. D.: The Treatment of the Patient with Severe Burns, *J. A. M. A.* **113**:1808-1812 (Nov. 11) 1939.

17. Mason, M.: Local Treatment of the Burned Area, *Surg., Gynec. & Obst.* **72**:250-253, 1941.

18. Aldrich, R. H.: Preoperative and Postoperative Treatment, Philadelphia. W. B. Saunders Company, 1937, pp. 256-287.

compound fracture or a laceration. The surgical principle is the same, though the specific methods are different.

Although the burned area may be sterile immediately after the accident, it is usually contaminated before the patient reaches the hospital. Most burns fall heir to some salve or grease. It is a great help to receive the patient with a sheet, towel or blanket over the burn instead of a greasy dressing which takes time to remove. This procedure of cleansing is essential in the successful treatment of burns regardless of the agent subsequently to be used.

*Method of Cleaning.*—After shock treatment has been instituted and the patient is responding, the cleaning of the burned area is begun. The patient should be removed to a suitable room for this purpose. There, under aseptic precautions—gloves, mask, cap, gown—the area should be cleaned as quickly, thoroughly and gently as possible. A scrubbed team of two or three will expedite the procedure. Depending on the foreign substance present, e. g., tar, grease and clothing, the areas are cleansed with soap, water or ether, with soft gauze or cotton pledgets. After thorough cleaning and removal of gross debris, the blisters are opened, and the redundant skin is removed.

The employment of anesthesia in cleaning depends on individual preference and the condition of the patient. Anesthesia has been employed in selected cases for some patients of this series, especially for excited unruly children. Light pentothal sodium is the anesthetic of choice. For adults, morphine and barbiturates have proved adequate in most cases. As Aldrich<sup>1</sup> pointed out, ether applied directly to the burned area does not hurt as much as one might suppose. The area of the burn is estimated and charted after the method of Berkow.<sup>19</sup>

#### TREATMENT OF THE BURNED AREA WITH VARIOUS AGENTS

Since records have been available, literally hundreds of different agents have been advised. The history of the treatment of burns by the ancients and others through the nineteenth century would in itself make an interesting narrative. Thus, it is not the purpose of this paper to favor any particular agent or to give credit to any single method, since splendid results are being obtained at different clinics with various agents. As a caution to those who may read without question of the claims made for various agents, it is well to remember that it is difficult if not impossible to make a satisfactory comparison between groups of cases in which the degree of shock, the degree of the burn and the area involved may differ so widely. Regardless of the agent employed,

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19. Berkow, S. G.: A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) Based on Surface Area Proportions, Arch. Surg. 8:138-148 (Jan., pt. 1) 1924.

destroyed tissue must be replaced by scar or graft, and no agent will do this. The purpose of any agent is to serve as a protective and an antiseptic scaffolding under which epithelial proliferation may take place.

Today agents for treatment can be generally classified under salves, ointments, pastes and jellies and eschar-producing and noneschar-producing solutions. For severe burns, eschar-producing solutions are more widely used. However, some clinics use sterile petrolatum or ointments, even for major burns. Of all agents used, tannic acid preparations in

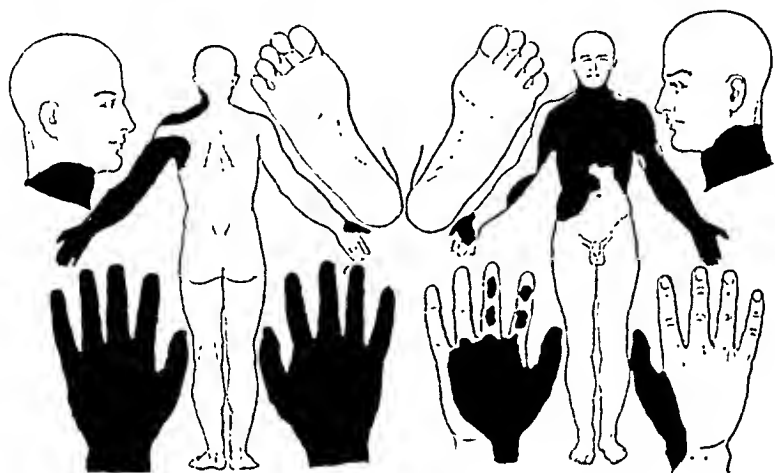


Fig. 1.—Reproduction of a printed form used to record blood studies and the area burned, using the Berkow estimations of skin surface.

Lower extremities (including buttocks) .....	38 per cent	Foot (one sixth of lower extremity) .....	3 per cent
Trunk (including neck)....	38 per cent	Lower leg (one third of lower extremity).....	6-7 per cent
Upper extremities.....	18 per cent	Thigh (one half of lower extremity) .....	9-10 per cent
Head .....	6 per cent	Total area burned.....	40 per cent
Hand (one fourth of an upper extremity).....	2-3 per cent	Combined 2d and 3d degree.	40 per cent

A. S. White man	48	Gasoline	Admitted: 6-2-41	Discharged: 11-5-41
	6-2-41		6-3-41	6-4-41
	12:05 a. m.	4 a. m.	4 p. m.	8 a. m.
Hematoerit.....	52	49	48	47
Hemoglobin .....	128	112	106	104
Red blood cell count	5.40	6.02	5.21	.....
Protein .....	8.7	7.11	.....	5.26
Nonprotein nitrogen.	55	36	.....	39
Treatment: 6-2-41	Plasma 2,500 cc.—total 4,000 cc. fluids by mouth and infusion			
6-3-41	Plasma 900 cc.—total 1,200 cc. fluids by mouth and infusion			
6-4-41	Plasma 500 cc.—total 3,100 cc. fluids by mouth and infusion			
By blood culture: 6- 7-41	Bacillus coli			} Both septicemias responded to chemotherapy
6-17-41	Staphylococcus haemolyticus			
Operations:	Five stages of skin grafting; also amputation of left hand.			

various percentages and forms are undoubtedly the most popular. Chief among eschar producers are tannic acid alone<sup>4</sup> or tannic acid followed by silver nitrate,<sup>20</sup> gentian violet, the triple dye mixture<sup>18</sup> and lately sulfadiazine (2 - [paraaminobenzenesulfonamido] - pyrimidine) spray. Many agents are available, each with its particular advantages and disadvantages. However, one surgical principle is essential to remember, that only a sterile nonirritating preparation should be applied to a surgically cleaned burned area.

*Method of Treatment.*—Burns at this clinic are not consistently treated with eschar-producing agents, but when their use is elected, the triple dye mixture of Dr. Robert Aldrich of Boston is employed. The dye mixture consists of gentian violet, brilliant green and acriflavine. The dye was chosen because it has a high specificity against gram-positive and gram-negative organisms as well as the ability to form, if properly applied, a thin pliable eschar.

The mixture does not deteriorate over a long period of time. In comparison with tannic acid, it is more expensive and more soiling, and the eschar takes longer to dry. On the other hand, the dye is more antiseptic and forms a thinner and more pliable eschar, under which infection is easier to detect. The dye can readily be removed from the person of the nurses or the operators with aromatic spirit of ammonia.

The technic employed is much like that of tannic acid application. After thorough gentle cleansing of the involved areas, the dye mixture is applied by sterile cotton pledgets six to eight times at twenty minute intervals. The patient is then transferred to a sterile bed. A cradle is placed over the bed, and heat slightly above 40 C. is maintained by electric bulbs. The drying of the eschar at times takes as long as twelve to eighteen hours, and every effort is made to keep the patient from contamination during this period. The pain is relieved after the first or second coating as with any other agent. The resultant eschar is deep purplish black with a gold-green sheen.

After the application of the dye, the treatment calls for constant vigilance. The proper diet and administration of fluids are maintained. Frequent inspection of the burned areas and recordings of the pulse rate and the temperature are essential, as well as frequent blood examinations. In ideal cases, if a small area of the back, the chest, the abdomen or an extremity is involved, sterility is usually easy to maintain. Unfortunately, however, these cases are infrequent. Burns around certain body orifices make infection inevitable, but the infection can be detected in the eschar, usually within twenty-four to forty-eight hours. The eschar becomes soft and moist, loses its sheen and changes to a

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20. Bettman, A. G.: Tannic Acid and Silver Nitrate in Burns, Surg., Gynec. & Obst. 62:458-463, 1936.

lighter blue. It can be removed with little difficulty. The infected area may be soaked with warm saline compresses for twenty-four to forty-eight hours and the dye reapplied without sacrificing the entire eschar.

An especial note of caution is directed to those who employ tanning agents—these solutions should never be used on the eyelids, the fingers, the hands or the toes. Ectropion is a common sequel. Venous and lymphatic obstruction by compression of vessels between an eschar and close underlying bone results in chronic dactylitis and deformity. After the usual cleansing, the fingers, the face and the toes are treated with gauze impregnated with bismuth tribromphenate. The digits are carefully covered separately so that burned surfaces are not in apposition. They are dressed only once every seventy-two hours unless they become infected. In this event, sterile saline compresses are used; these are removed down to the tissue every four hours until the infection has abated.

In burns about the face, the eyes should be examined thoroughly as soon as possible lest they close by edema. Regardless of the presence or absence of scleral or corneal injuries, the pupils are dilated with several drops of 1 per cent atropine. If injury is present, consultation is requested. Patients must be assured that they are not blind but that the lids are swollen shut. The edema usually persists seven to ten days before the lids function properly. During this time no attempt is made to pry open the lids for instillations. As the edema subsides, the conjunctivas are irrigated if necessary. Due to the orbicularis reflex, the eyes are not as a rule seriously injured.

#### REMOVAL OF THE ESCHAR AND EPITHELIZATION WITH OR WITHOUT GRAFT

There is no arbitrary day set for the removal of the eschar. The removal depends on the degree of the burn and the state of the eschar. i. e., whether infected or not.

If the burn is mainly second degree with only scattered small areas of greater depth and the crust has not become infected, the eschar is allowed to remain until complete healing has taken place. If it is allowed to remain, the eschar may begin to loosen and curl at the margins eight to fifteen days after the application of the agent. At this time, perhaps only  $\frac{1}{4}$  to  $\frac{1}{2}$  inch (0.6 to 1.3 cm.) of the border may become loose. If this occurs, the loose border is removed with sterile scissors and forceps, and the underlying new tissue is painted with a 5 per cent aqueous solution of gentian violet. At other times when the margin of the eschar loosens a considerable area (10 by 15 cm.), it may be removed and the underlying tissue may be found to be covered with

a layer of yellow fatty-looking material. The material may be mistaken for pus, which it is not. The material is plasma that has escaped after the agent was applied and has become concentrated under the eschar. It must be remembered that patients are treated for burns after they respond to shock therapy but not necessarily after they are cured of the shock. So, at times, leakage of body fluid continues after application



Fig. 2.—W. G., aged 18 months, was scalded by water. *A*, appearance of the eschar ten days after the burn. *B*, appearance after removal of the eschar eighteen days after the burn. *C*, appearance on the day of discharge, thirty-two days from the time of admission

of the eschar. This, too, is thought to be the reason for the wrinkled, ballotable eschars that sometimes occur, and they should not be removed simply because pus is suspected as the cause for their elevation unless there are other indications. This yellow material can be easily removed in twenty-four hours by compresses, after which some stimulating gauze



impregnated with bismuth tribromphenate or ointment of scarlet red is applied for several days until healing is complete.

If the burn is predominantly third degree, the eschar is electively removed from the fifth to seventh day after application of the dye with the patient under anesthesia. This time is chosen in order to allow the



Fig. 3.—A. S., aged 48 years, was burned by gasoline on June 2, 1941. *A*, appearance of the eschar four days later. The eschar was removed eleven days after the accident. The underlying tissue was treated with warm saline compresses for five days and then grafted. *B*, photograph taken fifteen days after grafting. *C*, photograph taken thirty-five days after grafting.

patient to recover from shock. The eschar is removed aseptically in the operating room. Sterile bandages are applied snugly for one night. The following day they are soaked thoroughly with sterile solution of

sodium chloride and removed. Compresses are then applied regularly until the tissue is suitable for grafting, usually within two to four days. The importance of early grafting in third degree burns cannot be over-emphasized.

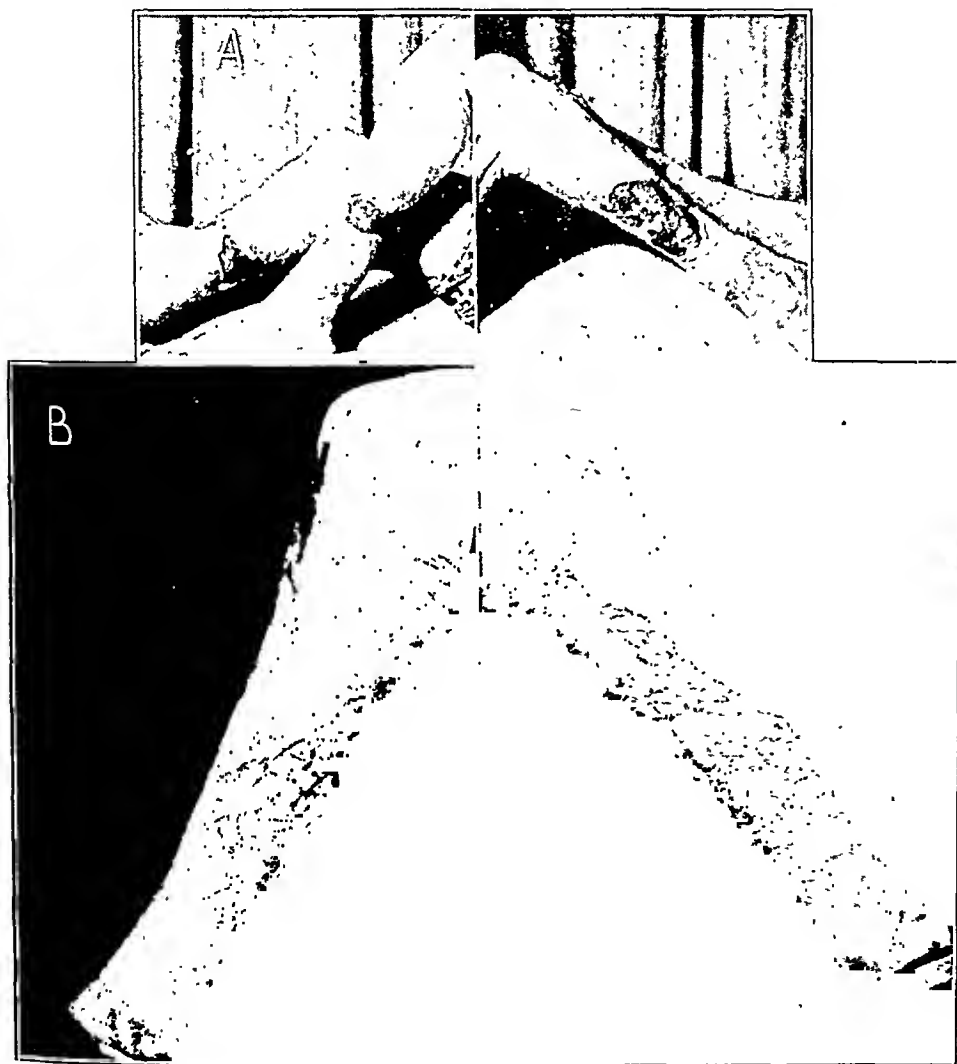


Fig. 4.—W. M., aged 31 years, was burned by gasoline six years before admission. *A*, indolent ulcers at the time of admission. *B*, end result nine months later.

If the eschar in second or third degree burns becomes infected, it should be removed and the underlying area treated with compresses until granulation appears suitable for grafting. If the area is large, grafting may be performed in several stages; in these cases, the Davis or small deep graft is usually employed. Between stages, exuberant

granulations are controlled with copper sulfate crystals or a saturated solution of copper sulfate, which is less damaging to epithelial buds than silver nitrate. Ordinary alcoholic antiseptics are not employed because they retard the healing process. Only aqueous preparations are used.

A severe burn under ideal circumstances may necessitate three to five months' hospitalization—much longer if grafting is delayed. Large wounds allowed to granulate may heal after months of daily dressings, only to break down again at the slightest strain on the new inelastic

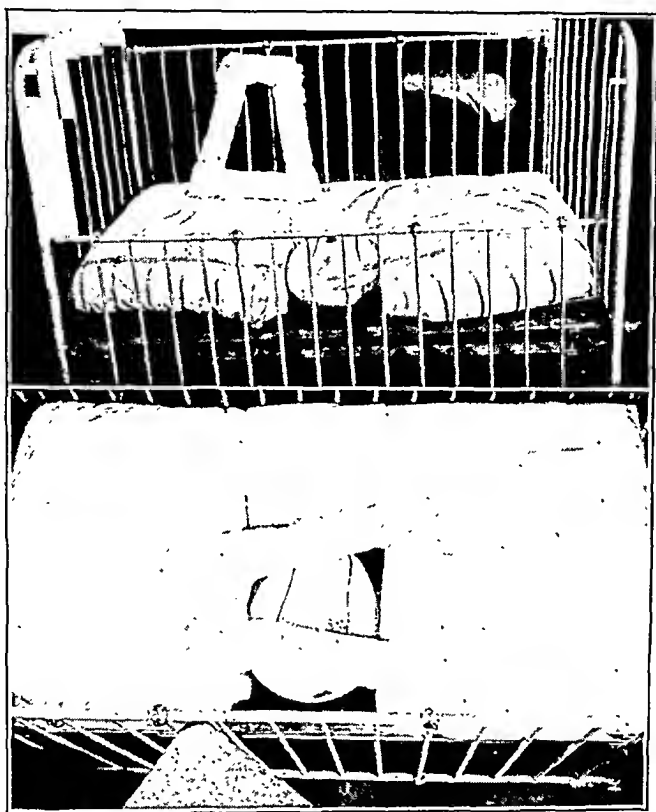


Fig. 5.—Two views of the crib, the mattress, the padded splint and the bedpan used in treating infants and young children with burns of the posterior surfaces of the body and the extremities.

scar. This is especially true of the lower extremity, where dependent mechanical elephantiasis develops in addition to indolent recurrent ulceration. These disabling complications can be forestalled by early grafting. Late grafting may even produce good functional results but under less favorable circumstances.

The stage between removal or peeling of the eschar and final healing is little discussed; this is justifiable, since patients rarely follow a regular

charted course. This stage can be fraught with many complications, such as resistant secondary anemia, septicemia, pneumonia, local coc-cogenous infection, indolent granulations, pyocyanus infection and psychoses. Ideally, a patient with a second degree burn might be discharged cured in twenty-one days; but if complications ensue, death may occur, or healing may be prolonged for weeks. Only those who follow the cases day by day can appreciate this long and at times discouraging stage of treatment.

#### COMPLICATIONS

There are three theories as to the so-called toxic phase accompanying severe burns: (1) the physical theory, in which the toxic course is thought to be due to fluid imbalance; (2) the old specific toxic theory of absorbed foreign protein, exploded by Underhill<sup>3</sup>; (3) the bacterial theory, which supports infection as the only cause. This question is a mooted one and will not be reviewed in this paper, but in my observations, I have never seen a septic course in the absence of infection.

*Anemia.*—Anemia of the secondary type is specifically noted because of its constant presence in severely burned patients and because of the necessity of its correction to induce healing. Anemia becomes more troublesome after the eschar is removed and large granulating areas are exposed. Before, after and between stages of grafting, continuous attention must be paid to the blood picture. This is especially true of children. A complete blood picture should be made at least once a week, and treatment of the anemia should be made by oral medication or transfusion. Grafting should not be performed on a patient with a hemoglobin value under 75 per cent. As much care should be given to maintain blood levels and vitamin concentration in patients with burns as in any other patients hospitalized for long periods.

*Septicemia.*—Septicemia is always a lurking danger when large areas of tissue are exposed to infection. It may occur either early in spite of meticulous cleansing or late between stages of eschar removal and grafting. Again, it may occur when eschars become infected. Any sudden rise in temperature with or without chill should indicate the immediate withdrawal of blood for culture. One patient in the present series had positive blood cultures on two occasions in a six week period—colon bacillus on the first and *Staphylococcus haemolyticus* on the second occasion, both times responding to chemotherapy. Another patient had a blood culture positive for infection with *Bacillus pyocyanus* from which he succumbed on the thirty-ninth day of the burn. The early recognition of this complication and treatment with chemotherapy will save lives.

*Pneumonia.*—Pneumonia complicating a burn is a serious and often fatal disease. Anoxia, fluid imbalance and pain, with shock, together with drugs administered for their relief may so retard respiration as to encourage early atelectasis and bronchopneumonia. Pneumonia may be an early or late complication. In children particularly, it runs a rapid and fatal course in spite of oxygen and chemotherapy. In this series, 4 of the 12 deaths were due to pneumonia. Of the 4 patients, all were under 4 years of age.

*Persistent Coccogenous Infection.*—Persistent coccogenous infection with resulting indolent granulations, more prevalent in older patients, can usually be traced to some general systemic cause. In cases in which heavily infected granulations do not progress normally, the red blood cell count and the hemoglobin and the protein content should be thoroughly examined; vitamin intake estimations and dietary studies should be checked. If the general condition is found satisfactory, attention is directed to the local tissue. With the patient under anesthesia, the tissue and the surrounding skin are painted with tincture of iodine. In addition, the granulations are painted with one application of saturated silver nitrate and then excised with a scalpel. Hot saline compresses are applied until bleeding is controlled, and ether is poured over the denuded area to aid drying and cleansing. The area is grafted at the same sitting. In some instances, this procedure will promote epithelization promptly. In other instances it must be repeated.

*Pyocyaneus Infection.*—Infection by *B. pyocyaneus* of the areas during epithelization has been a frequent complication in ward cases. It can quickly be eliminated by applying gauze dressing saturated with 3 per cent acetic acid to the area for twelve hours. This will eradicate the organism for indefinite periods and can be reapplied in case of reinfection. This treatment will not kill or hinder the growth of grafts.

*Urinary Suppression.*—Urinary suppression is most frequently seen in older patients during the first several days of the shock stage. In this series it has not been common. The treatment consists of giving concentrated dextrose intravenously and solution of sodium chloride by infusion if possible. The urine should be examined at least twice a week, even in the absence of urinary suppression, especially when wound infection is present. When the triple dye mixture is used as the therapeutic agent, false positive bile urine reactions may be present for some days owing to the absorption of the brilliant green from the mixture.

*Fever.*—Fever that is persistent in burned patients can usually be traced to infection. It is not unusual to find small infected lesions (10 by 5 cm.) that produce temperatures of 101 to 103 F. Constant daily inspection is necessary to eliminate this annoying indication of general systemic reaction. However, if the examination is thorough, an infected area can usually be found within twenty-four hours.

*Mental Reactions.*—The mental reactions of burned patients should not be ignored. Fear of pain and disfigurement are the patient's chief source of concern. Protracted hospitalization may be the cause of depression and melancholia, even to the point of desire for death. As soon as the condition of the patients will permit, a frank discussion of the condition is held. If the patient's mentality permits, the course of treatment is roughly outlined. It is not wise to underestimate the time necessary for cure. An occasional word of encouragement is helpful. Sources of physical irritation should be minimized. Dressing should be performed slowly and painstakingly and, if possible, by the same doctor on every occasion. Anesthesia should be employed in the removal of eschars, and compresses, when used, should be warm, not hot. The morale of the patient is dependent to a marked degree on the kindness, gentleness and prudent care of the physician.

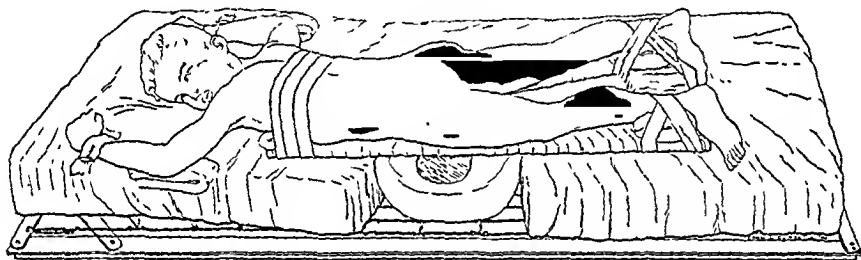


Fig. 6.—Illustration of the method of restraint and the use of the splint and the special mattress in treating burns of the posterior aspect of the body in infants and young children.

#### PREVENTION OF CONTRACTURES AND FOLLOW-UP WITH OR WITHOUT PLASTIC RECONSTRUCTION

Suspicious contracture areas are considered immediately after the burn has been treated. When possible, splints or other devices are used to prevent or minimize the resultant scar. It is not always possible, however, to use splints or casts because of circumferential burns which need frequent dressings. In such cases, the prime consideration is epithelization of the area and plastic reconstruction later. Measures for contracture prevention may tax the physician's ingenuity to the utmost. In infants and young children the spread eagle splint has been found to be of great aid in treating burns of the back, the buttocks and the posterior portions of the lower extremity. This splint of basswood is cut to individual pattern, well padded and strapped to the child. The child is then placed face down on a basal metabolism mattress. From the first, the removable portion of the mattress is withdrawn, and a bed pan is inserted to catch the excreta. At intervals of five to seven days, the splint is changed. Some patients are treated in this manner until complete healing has taken place.

On discharge, the patient is instructed in the care of the new epithelium. Daily massage with castor oil is of aid to prevent drying, scaling and itching. Bland nonirritating soaps should be used. Care should be exercised in exposing the new covering to sun, wind and cold. At this clinic, where burns are assigned to the surgical service, the responsibility remains with that service until the burn is epithelized,

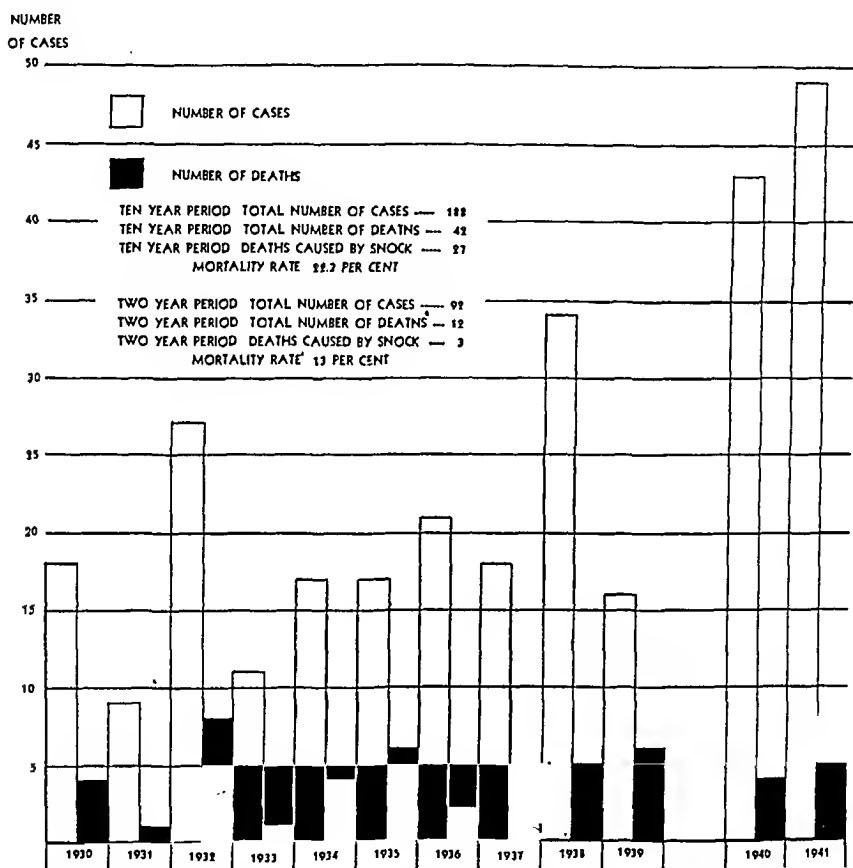


Fig. 7.—Graph showing the number of patients with burns admitted and the number who died from burns at the University Hospital in the past twelve years.

which may include grafting. Procedures of reconstruction or release of contractures are assigned to the department of plastic surgery. Patients are instructed to report for examination semiannually, especially children, in whom contraction may develop with growth.

#### STATISTICAL REVIEW

The review of cases includes the admissions in the period from March 1939 to November 1941; these comprise 92 patients.

Patients with burns make up only 0.014 per cent of the total admissions to the general surgical service. Of the 92 patients, 63 were male and 29 female. The industrial patients were all males. Seventy-five were white, and 17 were Negroes.

It is of economic interest to note that of the 92 patients, 56 were charity; 32 were compensation, and 4 were private. The age range was from 14 months to 64 years. All of the industrial patients were over 21 years of age. Of the 56 free patients, 35 were children of 10 years or under.

The causative agents were either scalding water or flames (from house fire, bonfire, gasoline, oil, gunpowder or gaseous explosions).

### Mortality Statistics

Case	Age of Patient	Cause of Burn	Area Involved, per Cent	Time of Death After Accident	Autopsy	Agent Used	Cause of Death *
1	22 mo.	Boiling water	45	23 days	....	Escharotic	Bronchopneumonia
2	3½ yr.	Boiling water	25	46 days	....	Escharotic	Bronchopneumonia
3	25 yr.	Flame (gasoline)	40	5 days	Yes	Escharotic	Pulmonary edema
4	47 yr.	Flame (gasoline)	48	33 days	....	Escharotic	Pyocyaneus septicemia
5	6 yr.	Flame (gas stove)	57	11 days	Yes	Escharotic	Pulmonary edema
6	50 yr.	Flame (oil stove)	90	3 days	Yes	Escharotic	Shock
7	3 yr.	Flame (gas stove)	27	25 days	....	Escharotic	Bronchopneumonia
8	6½ yr.	Flame (house fire)	48	12 hrs.	....	Escharotic	Anesthetic
9	5 yr.	Flame (oil)	50	4 hrs.	Yes	Ointment	Shock
10	4 yr.	Flame (house fire)	15	10 days	....	Escharotic	Bronchopneumonia
11	20 mo.	Boiling water	65	2½ hrs.	....	Escharotic	Shock
12	3 yr.	Flame (gasoline)	68	10 days	....	Escharotic	Intravenous sodium bicarbonate to combat acidosis

\* Summary of deaths: The causes were: pulmonary complication in 6 cases; shock in 3; septicemia in 1; anesthetic in 1, and intravenous reaction in 1. Three cases are open to criticism. Anesthesia should never have been used in case 8. This was poor judgment; the patient never reacted from the anesthetic. In case 11 there was a bad error in judgment. The child was not treated for shock before the treatment of the burn was considered. In case 12, death occurred six hours after the intravenous use of sodium bicarbonate in treating acidosis, and no other cause was found for the death.

No chemical or electric burns were included in this series. The time spent in the hospital varied from fifteen days to six months. The body area involved varied from 12 to 90 per cent by Berkow's standard of estimation. Of the 92 patients, grafting was done on 17. The number of graftings varied from one to five stages on the same patient. The small deep graft of Davis was used in all cases; in addition Thiersch grafts were used in 2 patients.

*Mortality Figures.*—In the decade 1930 to 1939 at the University Hospital there were treated 188 thermal burns with 42 deaths—a mortality rate of 22.3 per cent. In the past twenty-one months there were treated 92 patients with 12 deaths—a mortality rate of 13 per cent.

It is interesting to note that in the 42 deaths of the previous decade, 27 occurred within the first seventy-two hours from shock, while in the



present series only 3 died from shock. Had these 27 patients lived through the shock period there might conceivably have been a mortality rate of only 8 per cent. These figures would then show that shock therapy with the use of plasma has lowered the mortality rate but that the treatment of burns or burn complications has improved but little. Of the 12 deaths in the last series, 8 or 75 per cent occurred in children 6 years of age or under.

#### SUMMARY AND CONCLUSIONS

Three surgical principles are emphasized in the treatment of burns: (1) the primary treatment of shock before considering treatment of the burned area; (2) the recognition of a burn as an open contaminated wound, which should be properly cleaned before treatment; (3) the choosing of a sterile and nonirritating agent for the treatment of the burned area.

Patients with severe burns when first seen should be given morphine, should be wrapped with some covering (no greasy preparation should be applied to the burn) and should be sent as rapidly as possible to a hospital where proper shock therapy can be given.

Plasma therapy in the treatment of shock due to burns has, as in this series, definitely lowered the mortality rate. Infants and children are particularly labile as regards shock and should be treated for it whether or not they exhibit clinical signs. Though the reported mortality rate of 13 per cent is in no way remarkable, deaths from shock have dropped to 3 among the last 92 patients treated compared with 27 among the previous 188.

Cleansing of a burn should not be undertaken until the patient is responding well to shock therapy. Cleansing should be done under aseptic conditions as quickly, gently and thoroughly as possible.

Eschar-producing agents are preferred at this clinic for the treatment of burns involving multiple areas. They should not, however, be used on the fingers, the hands, the toes, the feet or the face. Agents do not replace destroyed tissue, and after their use the patient must be watched daily for all complications that can develop in the stage between the accident and the cure. Pneumonia complicating burns in infants and children has proved rapidly fatal in spite of modern therapy.

Patients with third degree burns can be spared many weeks in the hospital by skin grafting performed as soon as the condition of the patient permits.

It is a prediction that hospitalization for patients with burns will be prolonged in the future, because some of the severely burned patients who died from shock in the past will now be saved owing to improved methods in shock control.

# HEPATIC FUNCTION AND THE FORMATION OF HIPPURIC ACID

RESPONSE TO THE ADMINISTRATION OF AMINOACETIC ACID AND  
SODIUM BENZOATE IN PATIENTS WITH SUBNORMAL  
CAPACITY FOR SYNTHESIS

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In Quick's hippuric acid test, the benzoic acid administered as sodium benzoate brings two mechanisms into action in the liver: (1) the production of aminoacetic acid and (2) the conjugation of aminoacetic acid with benzoic acid to form hippuric acid. Quick<sup>1</sup> stated that the diminution of hippuric acid formation in patients is due mainly to the reduced ability of the liver to synthesize aminoacetic acid and in part to damage of the enzymatic mechanism performing the conjugation. This suggests that patients with diminished hepatic ability to furnish aminoacetic acid should respond with an increase in excretion of hippuric acid if aminoacetic acid is administered along with sodium benzoate. On the other hand, patients in whom the conjugation process also is impaired should not show such an increase.

## METHOD

To probe the validity of this assumption, we decided to determine the hippuric acid formation in patients to whom sodium benzoate was given with and without aminoacetic acid. Haines, Magath and Power,<sup>2</sup> studying patients with hyperthyroidism, performed this experiment on 8 of their subjects. They stated that their results were not consistent and proposed to study this problem further. In a previous article,<sup>3</sup> we reported the results of such an experiment in 5 normal subjects and in 6 patients with low excretion of hippuric acid. In the present

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This study was aided by the Louis M. Monheimer Research Fund.

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1. Quick, A. J.: Clinical Value of the Test for Hippuric Acid in Cases of Disease of the Liver, *Arch. Int. Med.* **57**:544 (March) 1936.

2. Haines, S. F.; Magath, T. B., and Power, M. H.: The Hippuric Acid Test in Hyperthyroidism, *Tr. Am. A. Study Goiter*, 1939, p. 277.

3. Probstein, J. G., and Londe, S.: Studies of Liver Function by Means of Quick's Hippuric Acid Test, *Ann. Surg.* **111**:230, 1940.

study we made observations on 24 additional patients whose excretion of hippuric acid was below normal. While the test was run for four hours on all of these patients, it was carried out for only one hour on the normal subjects in the studies previously reported. For purposes of adequate comparison, it was therefore necessary to perform the full four hour test on a few more normal subjects. The standard dose of 4 Gm. of sodium benzoate was used for the first test, while a mixture of 5 Gm. of aminoacetic acid and 4 Gm. of sodium benzoate was used for the second.

### RESULTS

As shown in table 1 and chart 1, the addition of aminoacetic acid caused a marked rise in the hippuric acid excreted during the first hour by 4 normal subjects; they were all able to eliminate 39 per cent or more of the ingested sodium benzoate in one hour. The character of the curve of the hourly rate of excretion also was changed, in that

TABLE 1.—*Effect of Ingestion of Aminoacetic Acid on Synthesis of Hippuric Acid in Normal Subjects*

Subject	With or Without Aminoacetic Acid	Percentage of Sodium Benzoate Excreted				Total
		First Hour	Second Hour	Third Hour	Fourth Hour	
1	Without.....	28	34	25	7	94
	With.....	45	37	7	0	89
2	Without.....	25	34	28	5	92
	With.....	42	27	0	0	69
3	Without.....	23	33	25	10	91
	With.....	40	35	7	0	82
4	Without.....	25	31	28	9	93
	With.....	30	27	6	0	72

the peak of hippuric acid synthesis appeared during the first hour, while it appeared during the second hour when sodium benzoate alone was taken. Interestingly enough, subject 2 eliminated no hippuric acid during the last two hours of his second test. Thus, despite the markedly increased output of hippuric acid during the first hour, this subject excreted only 69 per cent in four hours, as compared with 92 per cent when he took sodium benzoate alone. Subject 4 showed practically the same picture; he eliminated only 72 per cent in four hours after taking the aminoacetic acid-sodium benzoate mixture, as compared with 93 per cent after taking sodium benzoate alone.

These two observations, plus the fact that a number of patients to be discussed later behaved in a similar fashion, stimulated our interest in the possible reasons for this phenomenon. As one possibility, it may be assumed that while a part of the aminoacetic acid was used for conjugation with benzoic acid, another part was catabolized. The remaining free portion of the benzoic acid, then, may have been insufficient to

stimulate the liver to furnish a new supply of aminoacetic acid. However, we found that in 1 of our normal subjects a small dose of sodium benzoate (1 Gm.) exerted enough stimulus to enable him to eliminate 65 per cent of it in one hour.

Another possibility to be considered is that the aminoacetic acid-producing stimulus of the remaining benzoic acid may be inhibited by the deaminizing process which is set in motion by the ingested aminoacetic acid and which, gaining momentum, continues after deaminization is complete. We, therefore, in a series of experiments on 1 of the normal subjects, administered 1 Gm. of sodium benzoate at varying intervals after the ingestion of 5 Gm. of aminoacetic acid to provide benzoic acid

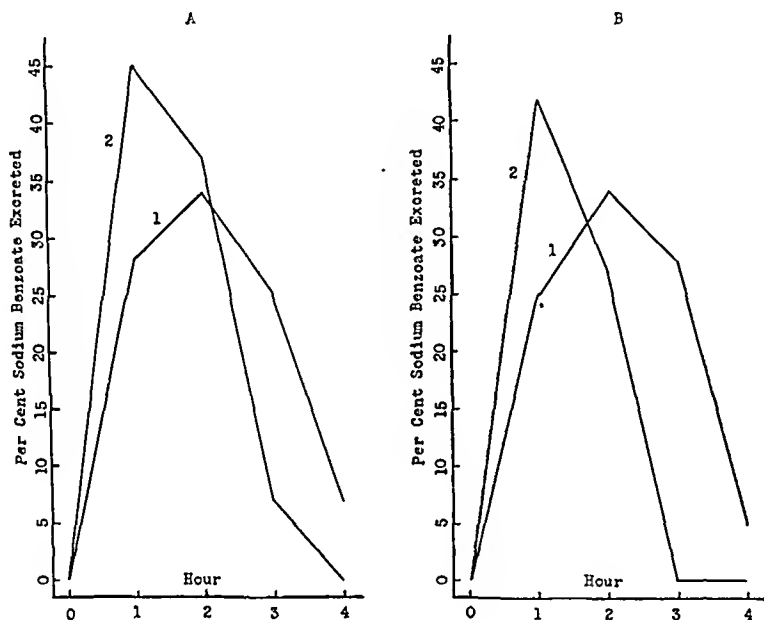


Chart 1.—Two types of response to the addition of aminoacetic acid in normal subjects. *A*, subject 1 (table 1): 1, after sodium benzoate; 2, after aminoacetic acid-sodium benzoate mixture. *B*, subject 2 (table 1): 1, after sodium benzoate; 2, after aminoacetic acid-sodium benzoate mixture.

in the blood during and after deaminization. However, at no time were we able to demonstrate a suppression of hippuric acid synthesis.

Still another factor which we have not investigated should be mentioned. In 1931, Quick<sup>4</sup> and, recently, Wagreich, Abrams and Harrow<sup>5</sup>

4. Quick, A. J.: The Conjugation of Benzoic Acid in Man, *J. Biol. Chem.* **92**:65, 1931.

5. Wagreich, H.; Abrams, A., and Harrow, B.: Detoxification of Benzoic Acid by Glucuronic Acid in Humans: Rate of Detoxification, *Proc. Soc. Exper. Biol. & Med.* **45**:46, 1940.

showed that in human subjects definite portions of ingested benzoic acid are excreted in conjugation with glycuronic acid. There is the possibility that the latter mechanism may be stimulated in some by ingesting aminoacetic acid and sodium benzoate, with the result that two reactions compete for the benzoic acid and the aminoacetic acid loses the contest.

Of the 30 patients studied, 5 (patients 1 to 5 in table 2 and chart 2) whose initial excretion of hippuric acid was low were unable to respond with an increased rate of hippuric acid synthesis after the administration of the aminoacetic acid-sodium benzoate mixture. A sixth patient

TABLE 2.—*Patients with Impaired Ability to Synthesize Hippuric Acid Who Did Not Respond with an Increase in Hippuric Acid Synthesis to the Ingestion of Aminoacetic Acid*

Pa- tient	Age, Yr.	Sex	Diagnosis	With or Without Aminoacetic Acid	Percentage of Sodium Benzoate Excreted				Total
					First Hour	Second Hour	Third Hour	Fourth Hour	
1	55	M	Portal cirrhosis*.....	Without	7	14	14	14	49
				With	3	23	16	8	50
2	46	M	Common duct obstruction; jaundice	Without	13	29	23	9	74
				With	16	22	28	8	69
3	63	F	Portal cirrhosis.....	Without	..	5*	4	4	13
				With	10	0	0	0	10
4	37	M	Diabetes; probable polycystic kidney; enlarged liver	Without	13	15	8	12	48
				With	18	15	9	10	52
5	48	M	Small liver; jaundice.....	Without	11	14	22	16	63
				With	10	14	20	..	44†
6	56	M	Duodenal ulcer with fistula of bile duct into the duodenum	Without	15	28	11	26	82
				With	15	32	26	7	80

\* Excreted in this and the preceding hour.

† Total for three hours only.

(patient 6, table 2), a borderline subject, showed an abnormal lag in the first two hours of his original test but excreted 82 per cent, a normal amount, in four hours. Adding aminoacetic acid did not overcome the lag, there being no increased response during the first two hours of the second test. Thus, in this patient, as in the first 5 mentioned, there was a defect in the conjugation process. This defect and a diminished ability of the liver to furnish aminoacetic acid were probably both responsible in patients 1 to 5, while in patient 6 only the conjugating mechanism was damaged, since the lag was not overcome by the addition of aminoacetic acid.

The remaining 24 patients all showed a rise in the rate of hippuric acid synthesis during the first two hours of the test with added amino-

acetic acid (table 3), but when we examined their excretion of hippuric acid during the entire four hour period, we found different types of response.

One type, represented by the largest group (patients 1 to 12), was like that of normal (or at least borderline) subjects when tested with sodium benzoate only. The patients were enabled by aminoacetic acid to eliminate 50 per cent or more of the ingested sodium benzoate (the excretion of only 1 remaining a little below this limit) in the first two hours. Ten patients in this group excreted 78 per cent or more in the four hour period. (The lower limit of normal with sodium benzoate alone is 80 per cent.) In every case the quantity of hippuric acid excreted during the first two hours and during the entire four hour period was

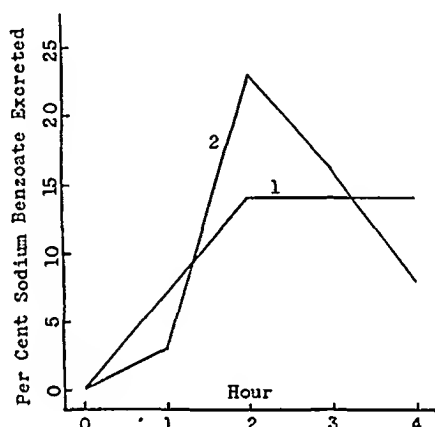


Chart 2.—Lack of response to the addition of aminoacetic acid in patient 1 (table 2) with impaired ability to synthesize hippuric acid: 1, after sodium benzoate; 2, after aminoacetic acid-sodium benzoate mixture.

definitely greater than when the patient was tested with sodium benzoate only (chart 3 *A*).

The second type (shown by patients 13 to 20, chart 3 *B*) was also the excretion of over 50 per cent of the ingested sodium benzoate during the first two hours when aminoacetic acid was given, but with considerable diminution of hippuric acid synthesis after this period. As a result, in 6 of these cases, the quantity of hippuric acid eliminated in four hours was no greater, and in some was even less, than when sodium benzoate alone was given. In the remaining 2 cases there was an increase in the four hour total, but not nearly so great as that seen in patients 1 to 12. Since the same kind of lag was observed in normal subjects, we cannot consider these patients to be more severely affected than those responding with a markedly increased four hour total.

TABLE 3.—*Patients with Impaired Ability to Synthesize Hippuric Acid Who Responded with an Increase in Hippuric Acid Synthesis to the Ingestion of Aminoacetic Acid*

Pa- tient	Age, Yr.	Sex	Diagnosis	With or Without Aminoacetic Acid	Percentage of Sodium Benzoate Excreted				
					First Hour	Second Hour	Third Hour	Fourth Hour	Total
1	50	M	Stricture of common duct, postoperative, still jaundiced	Without	17	20	22	6	65
				With	30	45	12	4	91
2	50	F	Stenosis of common duct; jaundice	Without	12	12	13	10	47
				With	27	32	20	6	85
3	32	F	Cholelithiasis.....	Without	12	20	21	10	63
				With	37	12	30	0	79
4	75	F	Subsiding cholelithiasis and acute cholecystitis	Without	6	28	11	0	45
				With	18	31	16	6	71
5	31	F	Cholelithiasis, obesity.....	Without	16	23	22	14	75
				With	38	34	9	0	81
6	20	M	Catarrhal jaundice.....	Without	11	15	19	15	60
				With	21	36	18	3	78
7	23	F	Hyperthyroidism.....	Without	..	15*	15	21	51
				With	26	43	..	14*	83
8	25	F	Hyperthyroidism.....	Without	..	10*	0	1	11
				With	38	42	5	0	85
9	56	M	Asthma.....	Without	20	31	16	7	74
				With	18	45	16	6	85
10	27	F	Paroxysmal hypertension; adrenal tumor (?)	Without	7	21	26	3	57
				With	16	44	17	1	78
11	81	M	Severe sunburn.....	Without	4	13	16	16	49
				With	24	20	10	15	75
12	49	F	Proliferative arthritis.....	Without	15	12	15	22	64
				With	45	36	7	3	91
13	38	F	Hemolytic icterus; splene- ctomy	Without	19	18	22	6	65
				With	28	35	4	0	67
14	46	F	Early hepatic cirrhosis; large liver and spleen	Without	11	21	8	7	47
				With	35	31	1	0	67
15	56	M	Cholelithiasis; bile duct ob- struction; jaundice	Without	13	0	34	18	65
				With	19	44	4	2	69
16	58	F	Cholelithiasis; bile duct ob- struction; jaundice	Without	15	14	20	0	49
				With	28	29	3	4	63
17	30	F	Hyperthyroidism.....	Without	19	26	17	5	67
				With	37	14	4	1	56
18	36	M	Hodgkin's disease.....	Without	24	34	13	2	73
				With	34	30	8	2	74
19	41	M	Advanced dementia paralytica, tabetic form	Without	17	14	19	16	66
				With	14	44	6	1	65
20	46	M	Chronic peptic ulcer.....	Without	15	22	28	7	72
				With	20	40	9	0	69
21	40	M	Arsphenamine hepatitis; jaundice	Without	4	13	9	22	48
				With	12	35	17	5	69
22	28	F	Exfoliative dermatitis.....	Without	17	17	18	14	66
				With	15	33	9	11	68
23	45	F	Carcinoma of the liver.....	Without	2	13	10	17	42
				With	3	29	15	9	56
24	70	M	Paget's disease; carcinoma of colon	Without	7	11	9	12	39
				With	17	8	33	14	72

\* Excreted in this and preceding hour.

The last 4 patients also showed a rise in the rate of hippuric acid synthesis but could not attain a 50 per cent elimination during the first two hours. The excretion during the entire four hour period also remained at a low level.

#### CONCLUSIONS

Normal adults taking 5 Gm. of aminoacetic acid and 4 Gm. of sodium benzoate eliminated more than 39 per cent of the sodium benzoate during the first hour after ingestion of the mixture. This rate of hippuric acid synthesis was much higher than that in the same normal subjects when they ingested 4 Gm. of sodium benzoate only. A marked drop in the

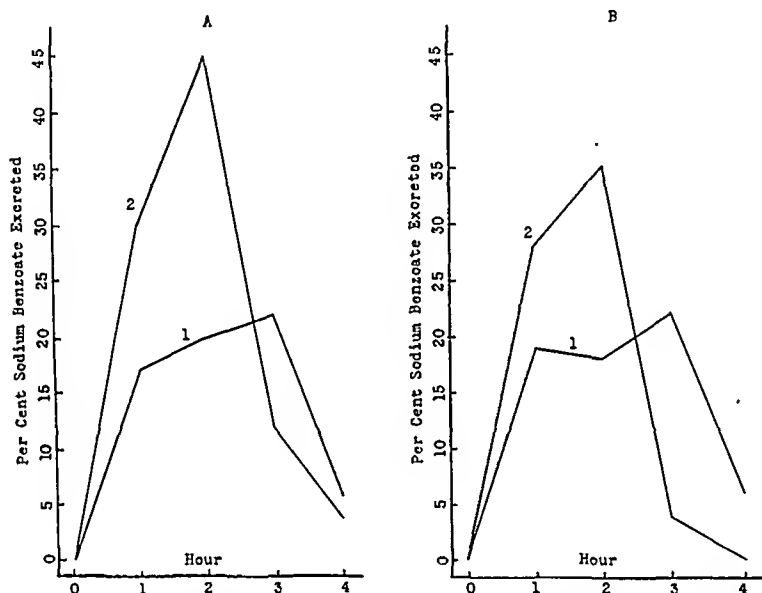


Chart 3.—Two types of increased response to the addition of aminoacetic acid in patients with impaired ability to synthesize hippuric acid. *A*, patient 1 (table 3): 1, after sodium benzoate; 2, after aminoacetic acid-sodium benzoate mixture. *B*, patient 13 (table 3): 1, after sodium benzoate; 2, after aminoacetic acid-sodium benzoate mixture.

excretion of hippuric acid occurred in the last two hours of the test in 2 of the normal subjects, so that the total amount eliminated in four hours was considerably less than that excreted when sodium benzoate alone was taken.

Six of 30 patients with impaired ability to synthesize hippuric acid showed no increase in the rate of synthesis when aminoacetic acid in addition to sodium benzoate was administered to them. Thus, definite impairment of the conjugation process was demonstrated in these patients.



The other 24 patients responded with a rise in the rate of hippuric acid synthesis during the first two hours. In these patients, it is concluded, the decreased elimination of hippuric acid during the standard four hour test was due mainly to a diminished ability of the liver to furnish aminoacetic acid.

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# PROTHROMBIN TEST AS A DIAGNOSTIC AND PROGNOSTIC AID

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During the past five years much has been written about vitamin K, and in many previous publications the causes of hypoprothrombinemia have been reiterated.<sup>1</sup>

It is not the purpose of this paper to review those causes but rather to present additional evidence to support the belief that the results of the prothrombin test are helpful in making an accurate diagnosis in the jaundiced patient. Also, in many instances a rough estimation of the extent of liver dysfunction can be determined. In addition, the results of the prothrombin test in 36 patients with intestinal dysfunction are presented to give further support to previous conclusions<sup>2</sup> that hypoprothrombinemia develops owing to lack of adequate food, loss of bile from the intestinal tract or a combination of the two.

The prothrombin test was carried out on 120 patients, most of whom had hypoprothrombinemia. The method employed was the one described by Quick,<sup>3</sup> and each time the test was used the thromboplastin solution was checked against normal plasma. Four to 8 mg. of 2-methyl-1, 4-naphthoquinone<sup>4</sup> (vitamin K) was usually given orally in divided doses over twelve to eighteen hours to patients for whom treatment was desirable. It is believed that it is better to give a large dose so that

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From the Department of Surgery, University Hospitals of Cleveland.

1. (a) Butt, H. R.; Snell, A. M., and Osterberg, A. E.: The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, *J. A. M. A.* **113**:383-389 (July 29) 1939. (b) Quick, A. J.: The Clinical Significance of Prothrombin as a Factor in Hemorrhage, *Pennsylvania M. J.* **43**:125-130 (Nov.) 1939. (c) Abbott, W. E., and Holden, W. D.: Hypoprothrombinemia in Intestinal Disorders, *Am. J. Surg.* **53**:215-218 (Aug.) 1941.

2. Clark, R. L., Jr.; Dixon, C. F.; Butt, H. R., and Snell, A. M.: Deficiency of Prothrombin Associated with Various Intestinal Disorders, *Proc. Staff Meet., Mayo Clin.* **14**:407-416 (June 28) 1939. Abbott and Holden.<sup>1c</sup>

3. Quick, A. J.: The Nature of Bleeding in Jaundice, *J. A. M. A.* **110**:1658-1662 (May 14) 1938.

4. Supplied by Eli Lilly & Co., Indianapolis.

the maximal response to the therapy can be determined in twenty-four to forty-eight hours. When patients were thought to have insufficient bile in the intestinal tract, 0.32 Gm. of bile salts<sup>4</sup> was administered with each 2 to 4 mg. of vitamin K.

The various types of cases are separated into groups for the sake of clarity.

#### LEUKEMIA

Five cases of leukemia were studied in which the initial prothrombin levels varied between 62 and 82 per cent. The average was 76 per cent of normal. Two of the patients were seen several years later and showed prothrombin amounts about 10 per cent below the former levels. Shortly afterward, both patients died, and autopsy revealed hepatomegaly with leukemic infiltration. Vitamin K therapy failed to produce any change in the prothrombin levels of these patients.

#### LAENNEC'S CIRRHOSIS

Twelve patients with Laennec's cirrhosis were studied; in most of these the condition was moderately far advanced. The initial prothrombin values ranged between 40 and 86 per cent of normal with an average value of 61 per cent. Many of these patients received vitamin K in adequate amounts and failed to show any response. The dose was then increased, and bile salts were administered, but still no response was obtained. In a patient who had a prothrombin level of 40 per cent, there was a gradual lowering to 25 per cent in a week, even though he received vitamin K. During this time, the icteric index was rising to 90, and the blood urea nitrogen was increasing. He died of hepatic insufficiency. In 3 cases, it was thought that exploration to rule out obstructive jaundice was indicated. The icteric indexes in these patients were 90, 131 and 140. The prothrombin tests revealed levels below normal, and the patients failed to respond to extensive therapy over three to six day periods. Because of this, it was believed that cirrhosis was present. Operation confirmed this impression in each instance. The bile ducts were patent and normal in size.

#### TUMOR OBSTRUCTING THE BILE DUCTS

There were 9 cases in which there was a tumor obstructing the bile ducts (table 1). In these, the prothrombin levels varied between 0 and 83 per cent. The average level was 43 per cent of normal. The 3 patients (table 1) with levels of 0, 10 and 21 per cent were bleeding when they entered the hospital. The first 2 responded well to therapy

with vitamin K and bile salts. This response was characteristic of almost the entire group. Patient 4 was admitted to the hospital for terminal care because of carcinomatosis with obstruction of the common duct due to extrinsic pressure. At the time of admission, the prothrombin level was 90 per cent of normal, and during the two ensuing weeks, it gradually fell to 31 per cent. After 2 mg. of 2-methyl-1, 4-naphthoquinone and 1.28 Gm. of bile salts were given, the prothrombin level returned to 96 per cent in twenty-four hours. It remained there or slightly above for three days without further therapy, and then during the next week fell to 70 per cent, at which time the patient died.

TABLE 1.—*Cases of Tumor Obstructing the Bile Ducts*

Case	Prothrombin Level, Percentage of Normal			Highest Icteric Index	Hours Be- tween Tests *	Treatment		Comment
	Initial	After Vitamin K	Final			Vita- min K, Mg.	Bile Salts, Gm.	
1	0	100	...	115	24	8	2.56	Bleeding from gums, bladder and gastrointestinal tract stopped with vitamin K
2	10	100	70	120	48	14	5.12	Hematuria stopped with vitamin K
3	21	...	...	130	..	0	0	Because of age and condition no therapy
4	31	96	70	120	24	16	1.28	
5	54	100	80	115	24	4	0.64	
6	60	92	100	45	14	6†	0	
7	64	50	50	43	48	8	1.28	Autopsy revealed hepatomegaly (4,500 Gm.) with biliary cirrhosis and metastasis
8	68	100	...	100	24	5†	...	
9	83	...	...	100	..	..	...	

\* Hours between initial prothrombin test and test after the administration of vitamin K.

† Given intravenously.

#### COMMON DUCT OBSTRUCTION DUE TO CALCULUS

The 13 patients with obstruction of the common duct due to calculus had prothrombin levels varying between 30 and 100 per cent of normal. The average level for the group was 75 per cent. In none of the cases was bleeding evident. The response to vitamin K was rapid (table 2), even though the biliary cirrhosis observed at operation was frequently severe.

#### STRICTURE OF THE COMMON DUCT

The 2 patients with stricture of the common duct had prothrombin levels of 16 and 26 per cent (table 3). Both patients had complete obstruction of the common duct of long standing and apparently had received some bile salts prior to admission, although they denied having

had medication of any kind during three weeks before they entered the hospital. In these cases the condition was more severe than in the two preceding groups. As was to be expected, the prothrombin levels were lower and the biliary cirrhosis more marked. Patients who have some bile entering the duodenum (stenosis without complete obstruction) naturally show higher prothrombin levels.

TABLE 2.—*Cases of Obstruction of the Common Duct Due to Calculus*

Case	Prothrombin Level, Percentage of Normal			Highest Icteric Index	Hours Be- tween Tests *	Treatment		Comment
	Initial	After Vitamin K	Final			Vita- min K, Mg.	Bile Salts, Gm.	
1	30	97	100	17	48	8	2.56	
2	41	92	100	60	24	8	1.28	
3	50	95	100	101	48	6	1.28	
4	50	90	72	65	48	4	0.96	Level decreased because of biliary drainage
5	75	100	88	45	18	8	0.64	
6	77	95	100	90	48	5†	0	Biliary cirrhosis marked
7	80	...	...	00	..	..	...	Patient refused operation
8	86	96	100	24	24	4	0.64	
9	87	100	100	29	24	4	0.96	
10	93	...	100	30	..	0	0	
11	100	...	100	45	..	0	0	Icteric for only 2 days
12	100	...	100	36	..	0	0	Partial and intermittent biliary obstruction
13	100	...	100	25	..	0	0	Intermittent mild icterus for 3 mo.

\* Hours between initial prothrombin test and test after the administration of vitamin K.

† Given intravenously.

TABLE 3.—*Cases of Obstruction of the Common Duct Due to Stricture*

Case	Prothrombin Level, Percentage of Normal			Highest Icteric Index	Hours Be- tween Tests *	Treatment		Comment
	Initial	After Vitamin K	Final			Vita- min K, Mg.	Bile Salts, Gm.	
1	16	100	...	120	20	8	1.28	Severe biliary cirrhosis
2	26	88	90	65	24	10	1.92	Severe biliary cirrhosis

\* Hours between initial prothrombin test and test after the administration of vitamin K.

#### BILIARY FISTULA

The 5 patients with biliary fistula (table 4) showed prothrombin levels between 35 and 93 per cent of normal with an average of 61 per cent. In this type of case, the prothrombin level usually varies directly with the duration of the fistula, provided hepatic damage has not been severe and the bile loss has been complete. The response to therapy with vitamin K and bile salts is usually uniformly good.

#### BURNS

The series of cases of burns is too small to be conclusive, but it seems that the prothrombin test should be useful in formulating a prognosis.

In table 5, patient 1 was admitted to the hospital and given the usual therapy for burns (débridement and tannic acid spray). The first blood sample, which was taken twelve hours after the patient had been burned, showed slight icterus; this gradually rose to 58 on the third day in the hospital, or the day prior to death. Twenty-four hours after admission, the patient began vomiting small amounts of blood. He gradually became confused and disoriented. His urinary output continued to be

TABLE 4.—Cases of Biliary Fistula

Case	Prothrombin Level, Percentage of Normal			Highest Icteric Index	Hours Be- tween Tests *	Treatment		Comment
	Initial	After Vitamin K	Final			Vita- min K, Mg.	Bile Salts, Gm.	
1	35	96	100	7	20	8	1.28	Biliary fistula for 3 to 4 mo. before patient entered hospital
2	45	...	100	17	..	..	...	Level rose gradually with 1.28 Gm. bile salts three times per day
3	64	98	100	29	48	4	0.96	Moderate biliary cirrhosis present
4	70	100	100	...	48	12	1.92	Patient had some bile salts before entering hospital
5	93	100	100	5	..	..	0.64	Bile apparently entered gastrointes- tinal tract until about 1 week before admission

\* Hours between initial prothrombin test and test after the administration of vitamin K.

TABLE 5.—Cases of Severe Burns

Case	Prothrombin Level, Percentage of Normal			Highest Icteric Index	Hours Be- tween Tests *	Treatment		Comment
	Initial	After Vitamin K	Final			Vita- min K, Mg.	Bile Salts, Gm.	
1	8	8	8	58	24	5	0	Autopsy revealed severe liver necrosis and blood in the gastro- intestinal tract
2	17	...	...	112	..	0	0	Autopsy showed severe liver necrosis
3	94	...	100	16	..	0	0	Icteric index fell to 6 with improve- ment

\* Hours between initial prothrombin test and test after the administration of vitamin K.

good, and the blood urea nitrogen determinations gave normal values. He was treated adequately with fluids and plasma but became more comatose, and hematemesis increased. On the third day in the hospital, the prothrombin level was 8 per cent of normal. Five milligrams of vitamin K was given intravenously without any effect on the prothrombin blood level. He died twenty hours later, and autopsy showed extreme necrosis of the liver and blood throughout the lumen of the gastro-intestinal tract. No one bleeding point could be identified, and no areas of ulceration were seen. In the second case, the prothrombin level fell to 17 per cent before the death of the patient, and at autopsy marked

TABLE 6.—Cases of Intestinal Disorders

Case	Prothrombin Level Percentage of Normal				Treatment			Diagnosis	Comment
	Initial	After Vitamin K		Hours Between Tests *	Vita- min K, Mg.	Bile Salts, Gm.			
		Final							
1	6	100	100	14	6	0.96	Intestinal obstruction .....	After 2 weeks of intestinal intubation profuse gastrointestinal bleeding started; it stopped with vitamin K	
2	18	82	100	24	8	0	Intestinal obstruction and postoperative intestinal fistula	Oozing of blood from wound on eighth postoperative day	
3	20	...	...	..	0	0	Perforated gastric ulcer; subphrenic abscess	On gastrointestinal suction and no food there was bleeding from wound; patient died before vitamin K could be given	
4	20	88	100	12	8	1.28	Strangulated ventral hernia.....	On intestinal intubation for 15 days there were bloody stools; bleeding was stopped with vitamin K	
5	21	75	100	22	4	0	High intestinal fistula.....	Bleeding from the wound stopped with treatment	
6	22	82	100	24	8	0	Pneumonia; peritonitis; Intestinal obstruction	Gastrointestinal bleeding and bleeding from wound responded to vitamin K therapy	
7	26	51	100	12	8	0	Intestinal obstruction .....	Prothrombin level of 100 per cent occurred 40 hours after vitamin K was given; Intestinal intubation used	
8	34	82	87	24	4	0.32	Appendicitis; term pregnancy, delivered; fecal fistula	Intestinal intubation used	
9	38	80	100	20	8	1.28	Low postoperative intestinal fistula..	Intestinal intubation used	
10	38	80	100	18	8	1.28	Adenocarcinoma of the stomach.....	Bleeding from wound was moderate on sixth postoperative day; gastric suction employed	
11	50	80	93	48	10	0	Appendicitis with perforation and peritonitis	Poor diet and gastric suction; bleeding from wound; blood transfusion prior to prothrombin test; no bleeding after administration of vitamin K	
12	60	...	95	..	0	0	Adenocarcinoma of the stomach.....	Gastric suction and no food; level returned to normal when food was given and suction stopped	
13	62	...	100	..	0	0	Carcinoma of the sigmoid; intestinal fistula	Had been on starvation diet	
14	66	...	85	..	0	0	Intestinal obstruction .....	Intestinal intubation for 6 days prior to test; level returned toward normal as food was given	
15	70	...	95	..	0	0	Perforated gastric ulcer.....	Twenty-one days of inadequate diet and intermittent gastric suction	
16	70	...	...	..	0	0	Diverticulitis of the colon.....	Severe diarrhea	

17	70	100	100	24	1	0	Intestinal obstruction .....	Intestinal intubation had been employed
18	72	...	100	..	0	0	Pyloric obstruction due to chronic granulomatous gastritis	Level determined 6 days after gastric resection returned to normal with food
19	74	..	100	..	0	0	Chronic gastric ulcer with pyloric obstruction	Preoperative level was 98 per cent; level fell with gastric suction and inadequate diet
20	75	...	100	..	0	0	Acute appendicitis with perforation and peritonitis	Two days after operation the prothrombin level was 92 per cent; it fell owing to lack of food and gastric suction
21	76	...	...	..	0	0	Carcinoma of the rectum and malnutrition	Inadequate diet; test made 13 days after operation
22	77	...	100	..	0	0	Carcinoma of the colon; low intestinal fistula	On poor diet
23	80	94	100	24	2	0.32	Chronic gastric ulcer with pyloric obstruction	Patient had marked vomiting prior to admission
24	86	...	...	..	0	0	Non-tropical sprue .....	Marked diarrhea present
25	88	...	100	..	0	0	Acute appendicitis; bleeding peptic ulcer	One day after appendectomy, the patient vomited 1,000 cc. of blood
26	90	...	...	..	0	0	Severe ulcerative colitis.....	Marked malnutrition and diarrhea
27	90	...	100	..	0	0	Carcinoma of the stomach with pyloric obstruction	After gastroenterostomy with inadequate diet and suction, level fell to 73 per cent
28	93	...	100	..	0	0	Intestinal obstruction; appendical abscess	Intubation and poor diet
29	93	100	100	24	4	0	Gastrocolic fistula .....	Patient showed marked weight loss
30	95	...	...	..	0	0	Partial intestinal obstruction; malnutrition	
31	100	...	...	..	0	0	Carcinoma of the stomach.....	Poorly nourished
32	100	...	...	..	0	0	Intestinal obstruction .....	Gastric suction was employed for 3 days; then diet was started; prothrombin level determined on fifth postoperative day
33	100	...	...	..	0	0	Non-tropical sprue .....	
34	100	...	100	..	0	0	Severe ulcerative colitis.....	Prothrombin levels taken 2 months apart during severe illness
35	100	...	...	..	0	0	Gastrojejunocolic fistula .....	Patient had lost 51 pounds
36	100	...	...	..	0	0	Duodenal ulcer with hemorrhage.....	

\* Hours between initial prothrombin test and test after the administration of vitamin K.



liver necrosis was again present. The third patient was a man who had been burned almost as extensively as either of the first 2 patients. His prothrombin level fell slightly when his icteric index was showing a slight rise; as he improved, both returned to normal.

#### INTESTINAL DYSFUNCTION

Thirty-six patients with intestinal dysfunction were studied. The prothrombin levels varied between 6 and 100 per cent of normal (table 6). A wide variety of cases is presented in this series, but for the most part the patients who showed the most profound changes were those with small intestinal fistulas or intestinal intubation. (Cases 1, 3, 4, 5, 6, 7 and 22 were previously reported at greater length, and a more complete discussion of this type of disorder was presented.<sup>1c</sup>) Usually, these patients show an adequately functioning liver, and the deficiency of prothrombin is due to an inadequate diet, loss of bile or a malfunctioning gastrointestinal tract.

#### MISCELLANEOUS CASES

Five patients with heart disease with decompensation showed levels between 55 and 94 per cent. In 2 of these, postmortem examination showed marked chronic passive congestion of the liver. Ten patients with severe gallbladder disease had prothrombin levels between 90 and 100 per cent, and it is thought that patients with uncomplicated cholecystitis and cholelithiasis rarely show values below this.

Four patients with hepatitis and 4 with catarrhal jaundice were observed; these showed levels ranging between 52 and 100 per cent of normal. Some of these patients responded to vitamin K and bile salts, and it was believed that the deficiency was due largely to the fact that although liver function was adequate, bile could not enter the duodenum because of the swelling causing intrahepatic biliary obstruction.

A patient with Weil's disease was tested. He had previously had fairly severe nasal hemorrhages, but unfortunately the first prothrombin level was obtained about one week later and was then 85 per cent of normal. Another patient with numerous congenital cysts of the liver had a prothrombin level of 81 per cent, and a patient with a bullet wound of the liver showed a prothrombin level of 92 per cent. Neither of these patients responded to vitamin K therapy.

Four patients were seen because of bleeding, and prothrombin levels were determined. For 2 of these patients, the diagnosis was thrombopenic purpura; for the other 2, hemophilia. Prothrombin levels of 100 per cent were found in each instance. A man receiving large amounts of heparin because of recent pulmonary embolus had a prothrombin level of 100 per cent, even though his clotting time was greatly prolonged.

Recently, Sheely<sup>5</sup> reported lowering of the prothrombin level in slightly less than 50 per cent of the tuberculous patients he studied. In the 4 cases in our series, 2 patients had severe recurrent pulmonary hemorrhages due to extensive tuberculosis of the lungs, and 2 had widespread miliary tuberculosis. Both of the patients with hemorrhage had prothrombin levels above the bleeding zone (85 and 97 per cent), but vitamin K was nevertheless administered. Hemoptysis was not altered in either case. In the 2 other patients with levels of 52 and 86 per cent, autopsy showed moderate liver disease along with diffuse miliary tuberculosis.

## COMMENT

In the cases presented, the patients with leukemia, cirrhosis and burns failed to show any response to vitamin K therapy owing to hepatocellular damage. In several instances, the prothrombin levels of patients with extensive tumor metastases to the liver with accompanying biliary cirrhosis did not show any improvement with adequate therapy with vitamin K and bile salts. Lord and Andrus<sup>6</sup> recently advocated the determination of the prothrombin blood level as an aid in differentiating intrahepatic and extrahepatic jaundice. Prior to this, Scanlon and associates,<sup>7</sup> Stewart<sup>8</sup> and other workers produced evidence to show that such diseases as cirrhosis, hepatitis and leukemia are accompanied by low prothrombin levels solely because of liver damage. Wilson<sup>9</sup> showed that in such cases the results of the hippuric acid test of liver function are closely correlated with the prothrombin blood level. Most of the numerous liver tests available today merely indicate the degree of liver function present; on the other hand, serial determinations of the prothrombin amount not only give one an idea of the degree of damage that may be present but also aid greatly in the differential diagnosis of intrahepatic and extrahepatic jaundice.

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5. Sheely, R. F.: Prothrombin Deficiency in Pulmonary Tuberculosis, *J. A. M. A.* **117**:1603-1606 (Nov. 8) 1941.

6. Lord, J. W., Jr., and Andrus, W. deW.: Differentiation of Intrahepatic and Extrahepatic Jaundice, *Arch. Int. Med.* **68**:199-210 (Aug.) 1941.

7. Scanlon, G. H.; Brinkhous, K. M.; Warner, E. D.; Smith, H. P., and Flynn, J. E.: Plasma Prothrombin and Bleeding Tendency with Special Reference to Jaundiced Patients and Vitamin K Therapy, *J. A. M. A.* **112**:1898-1901 (May 13) 1939.

8. Stewart, J. D.: Prothrombin Deficiency and Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, *Ann. Surg.* **109**:588-595 (April) 1939.

9. Wilson, S. J.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Human Subjects, *Proc. Soc. Exper. Biol. & Med.* **41**:559-561 (June) 1939.

Unless the liver function can be improved in cases with hepatocellular damage, the low prothrombin level will remain unchanged or decrease further, even though large quantities of vitamin K and bile salts are given.

Wolff, Elkinton and Rhoads<sup>10</sup> in studying cases of burns by various liver function tests showed a lowering of the prothrombin level corresponding to the decrease in the liver function. In their series, all the patients recovered, and none showed prothrombin levels in the bleeding zone. In cases of burns, therefore, it is thought that the prothrombin test is a rather accurate index of liver damage, and in the event that the prothrombin level decreases rapidly, the prognosis is grave. Such patients with liver necrosis will not respond to the administration of vitamin K.

Some patients with acute hepatitis and catarrhal jaundice show low prothrombin levels because of liver damage and apparently also because of obstruction due to congestion and swelling in the small intrahepatic bile channels. The extent and rate of response to vitamin K in such patients points out which factor is the most important. Although we have not seen a patient with hepatitis or catarrhal jaundice that progressed to acute yellow atrophy, it seems that the prothrombin level in such a patient should continue to fall and not respond to vitamin K therapy. In Weil's disease, the prothrombin level probably reacts similarly to the way it does in cases of hepatitis or catarrhal jaundice.

Practically all patients with biliary obstruction due to stone, tumor or scar tissue responded to adequate amounts of vitamin K in twenty-four to forty-eight hours. One patient did not, and 2 others who showed a normal response initially later failed to show a rise with adequate amounts of treatment. In all 3, autopsy revealed obstruction of the common duct with severe biliary cirrhosis and extensive liver metastasis. It is believed that the condition would have to be severe before only one of the two aforementioned disorders would result in persistent hypoprothrombinemia when vitamin K had been administered. In cases of mild or moderate involvement, the response to vitamin K might be slower than normal, but it should occur.

In patients with tuberculosis, it is probable that hemoptysis does not occur owing to hypoprothrombinemia, but it might be exaggerated when the blood-clotting mechanism is subnormal. In the cases presented, tuberculosis was severe, but, of course, the number is too small to permit any definite conclusions.

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10. Wolff, W. A.; Elkinton, J. R., and Rhoads, J. E.: Liver Damage and Dextrose Tolerance in Severe Burns, *Ann. Surg.* **112**:158-160 (July) 1940.

## CONCLUSIONS

A brief summary is presented of 120 cases which were studied during the past two and one-half years. The importance of keeping hypoprothrombinemia in mind in cases in which various types of intestinal disorders are present is stressed.

The prothrombin test, which can be simply done and is inexpensive, is an aid in determining the type of jaundice. It is necessary to study the patients carefully and repeatedly both before and after the administration of vitamin K and to be well acquainted with their complaints and physical findings in order that the results can be properly evaluated. In the series presented, it has been shown that patients with relatively severe liver damage do not respond to vitamin K therapy and that patients with common duct obstruction practically always respond to adequate therapy.

Finally, it apparently is a test which can help the physician determine the severity of liver damage in cases of burns, and it is thought that by serial examinations, an early and accurate prognosis can be formulated.

# EFFECT OF DESOXYCORTICOSTERONE ACETATE IN POSTOPERATIVE SHOCK

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In recent years there have been several attempts made to apply some of the experimental methods for the prevention of shock in animals to practical use in human beings. Many of these have taken the form of direct replacement of liquid to make up for the loss of circulating blood volume. Others have depended on the use of adrenocortical substances, for the value of which some observers<sup>1</sup> have made important claims.

That adrenocortical substances might have considerable value in the prevention or the treatment of shock is suggested by a large amount of clinical, pathologic and experimental data gathered by many different observers. Thus Short<sup>2</sup> suggested the theory that failure of the adrenal glands, which play an important role in the maintenance of vessel tone, precipitates the state of shock. Swingle and associates<sup>3</sup> showed that adrenalectomized dogs maintained in normal health and vigor by injections of adrenal cortical extract lapsed into circulatory collapse and shock following any trauma which put a strain on them. They suggested the similarity of the signs and symptoms of adrenal insufficiency and traumatic shock. Selye and associates<sup>4</sup> found characteristic changes in

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1. (a) Wilson, W. C.; MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds Under Modern Methods of Treatment, *Brit. J. Surg.* **25**:826, 1938. (b) Perla, D.; Freiman, D. G.; Sandberg, M., and Greenberg, S. S.: Prevention of Histamine and Surgical Shock by Cortical Hormone (Desoxycorticosterone Acetate and Cortia) and Saline, *Proc. Soc. Exper. Biol. & Med.* **43**:397, 1940. (c) Reed, F. R.: Acute Adrenal Cortex Exhaustion and Its Relationship to Shock, *Am. J. Surg.* **40**:514, 1938. (d) Besser, E. L.: Role of the Adrenal Glands in Shock, *Arch. Surg.* **43**:249 (Aug.) 1941.

2. Short, R., in Mekie, E. C.: *Handbook of Surgery*, Baltimore, William Wood & Company, 1936, p. 35.

3. Swingle, W. W., and others: Effect of Priming Doses of Desoxycorticosterone Acetate in Preventing Circulatory Failure and Shock in Adrenalectomized Dog, *Am. J. Physiol.* **132**:249, 1941. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: A Study of the Circulatory Failure and Shock Following Trauma to the Healthy Vigorous Adrenalectomized Dog, *ibid.* **124**:22, 1938.

4. Selye, H.; Dosne, C.; Bassett, L., and Whittaker, J.: Value of Cortical Hormones in Traumatic Shock and Allied Conditions, *Canad. M. A. J.* **43**:1 (July) 1940. Selye, H., and Dosne, C.: Changes (Hypochloremia and Adrenal Atrophy) Produced by Desoxycorticosterone Overdosage in Rat, *Proc. Soc. Exper. Biol. & Med.* **44**:165, 1940.

the adrenal glands during shock and showed the increased activity of the adrenal glands during recovery. The findings of Zwemer<sup>5</sup> and the results of Wohl and co-workers<sup>6</sup> also showed pathologic changes in the adrenal cortex in conditions associated with shock. Weil and Browne<sup>7</sup> found large quantities of adrenal cortical hormone in the urine of patients after operation; they interpreted this as suggesting an effort of these glands to overcome operative shock.

According to Thorn and associates,<sup>8</sup> Cleghorn and associates,<sup>9</sup> Levy Simpson<sup>10</sup> and Loeb and associates,<sup>11</sup> adrenal cortical hormone affects electrolyte and water metabolism. It causes striking retention of sodium salts with restoration of the blood sodium level to normal. It causes also retention of water with increase in plasma and interstitial fluid volume and consequent gain in weight. It lowers the serum potassium, at times to abnormally low levels, and temporarily increases the excretion of this ion. It restores renal function and increases the excretion of nitrogen when nonprotein nitrogen has been retained. It causes also a decrease in the concentration of total protein, calcium and cholesterol in the serum, probably because of hemodilution associated with an increase in plasma volume.

By the use of adrenal cortical extract, Heuer and Andrus<sup>12</sup> prolonged the lives of dogs in which shock was produced by the intravenous injection of aqueous extracts of obstructed intestinal loops. Menkin<sup>13</sup> reported that the increase in capillary permeability caused by inflam-

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5. Zwemer, R. L.: Study of Adrenal Cortex Morphology, *Am. J. Path.* **12**: 107, 1936.

6. Wohl, M. G.; Burns, J. C., and Clark, J. H.: Adrenal Glands in Dogs with High Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **33**:543, 1936.

7. Weil, P., and Browne, J. S. L.: The Excretion of Cortin After Surgical Operations, *Science* **90**:445, 1939.

8. Thorn, G. W.; Howard, R. P., and Emerson, K., Jr.: Treatment of Addison's Disease with Desoxycorticosterone Acetate, a Synthetic Adrenal Cortical Hormone, *J. Clin. Investigation* **18**:449, 1939.

9. Cleghorn, R. A.; Fowler, J. L. A., and Wenzel, J. S.: The Assay of Desoxycorticosterone Acetate and Its Use in the Treatment of Addison's Disease, *J. Clin. Investigation* **18**:475, 1939.

10. Levy Simpson, S.: The Use of Synthetic Desoxycorticosterone Acetate in Addison's Disease, *Lancet* **2**:557, 1938.

11. Loeb, R. F.; Atchley, D. W.; Ferrebee, J. W., and Ragan, C.: Observations on the Effect of Desoxycorticosterone Esters and Progesterone in Patients with Addison's Disease, *Tr. A. Am. Physicians* **54**:285, 1939.

12. Heuer, G. J., and Andrus, W. DeW.: Effect of Adrenal Cortical Extract in Controlling Shock Following Injection of Aqueous Extracts of Closed Intestinal Loops, *Ann. Surg.* **100**:734, 1934.

13. Menkin, V.: Effect of Adrenal Cortex Extract on Capillary Permeability, *Am. J. Physiol.* **129**:691, 1940.

matory exudates can be wholly or in part inhibited by the local injection of adrenal cortical extract and separately by desoxycorticosterone acetate.

McAllister and Thorn<sup>14</sup> found that the decrease in plasma volume during shock could be prevented in dogs by large intravenous doses of adrenal cortical extract. Fine and associates<sup>15</sup> showed that although a decrease in plasma volume was lessened in dogs subjected to a distention of the small intestine by the use of desoxycorticosterone acetate, the survival time was not appreciably increased. Wilson and co-workers<sup>1a</sup> reported favorable results from the use of adrenal cortical extracts in shock following burns.

McAllister<sup>16</sup> and, separately, Ragan and co-workers<sup>17</sup> showed that desoxycorticosterone esters administered three to six hours before operation prevent the usual decrease in plasma volume accompanying the administration of ether and surgical operations in dogs. Perla and associates<sup>1b</sup> expressed the belief that histamine shock in rats and mice could be prevented by treatment with adrenal cortical extract and solution of sodium chloride.

Such data naturally led to the application of the method to the treatment of shock in human beings.<sup>18</sup> The appearance of reports of the results (which will be discussed later) led us to try the method in selected operative patients.

There are obvious difficulties in establishing satisfactory criteria for the evaluation of the therapy. Many factors, such as the previous condition of the patient, the location and the extent of the lesion, the anesthesia, the duration of the operation, the amount of blood loss, the vomiting, the temperature, the degree of fluid loss by evaporation or diarrhea or emesis, contribute to the postoperative picture. The significance of blood pressure drop or the degree of hemoconcentration demands fractional evaluation of the amount of blood loss and of other fluid loss during and after the operation; both evaluations introduce large errors. In a recent discussion of the applicability of experimental results

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14. McAllister, F. F., and Thorn, G. W.: Effect of Adrenal Cortical Hormone on Reduction of Plasma Volume Resulting from Etherization, *Proc. Soc. Exper. Biol. & Med.* **36**:736, 1937.

15. Fine, J.; Fuchs, F., and Mark, J.: Effect of Desoxycorticosterone on Plasma Volume in Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **43**:514, 1940.

16. McAllister, F. F.: The Effect of Ether Anesthesia on the Volume of Plasma and Extracellular Fluid, *Ann. J. Physiol.* **124**:391, 1938.

17. Ragan, C.; Ferree, J. W., and Fish, G. W.: Effect of Desoxycorticosterone Acetate on Plasma Volume in Patients During Ether Anesthesia and Surgical Operation, *Proc. Soc. Exper. Biol. & Med.* **42**:712, 1939.

18. (a) Brown, J. J. M.; Dennison, W. M.; Ross, J. A., and Divine, D.: Experiences at a Casualty Clearing Station, *Lancet* **2**:443, 1940. (b) Footnote 1.

to the problem of shock in man, Wiggers<sup>19</sup> called attention to the desirability of establishing reliable criteria which indicate that a state has been produced which is similar to that observed in traumatic, surgical and toxic shock of man. He pointed out also that the term "shock" should perhaps be restricted to an irreversible state of circulatory failure.

Since the ultimate aim in the prevention of shock or its early recognition and treatment is the avoidance of death, we decided to use the mortality rate as the criterion of the efficacy of the therapy. This would give greater objectivity and enable us to avoid relying on clinical impressions alone. This is especially true if the use of the term "shock" is

TABLE 1.—*Distribution of Operative Procedures Performed on Control and Treated Patients*

Operation	Treated with Desoxy- corticosterone Acetate		Controls	
	Number	Deaths	Number	Deaths
Radical mastectomy .....	15	0	15	0
Gastrectomy .....	33	4	33	3
Abdominoperineal resection of rectum.....	11	2	11	1
Resection of colon.....	10	2	10	1
Ileosigmoidostomy .....	1	0	1	0
Colostomy .....	3	0	3	0
Obstructive resections .....	1	0	1	0
Resection for regional enteritis.....	5	1	5	1
Splenectomy .....	1	0	1	0
Thoracoplasty for tuberculosis.....	1	0	1	0
Nephrectomy for carcinoma.....	1	0	1	0
Perforated gastroduodenal ulcer.....	2	0	2	0
Cholecystenterostomy .....	2	0	2	1
Excision of retroperitoneal sarcoma.....	1	0	1	0
Thoracotomy for excision of sarcoma of the thorax .....	1	1	1	1
Cholecystectomy and choledochostomy with T tube; previous acute pancreatitis.....	1	0	1	0
Amputation of leg.....	1	0	1	0
Laparotomy for carcinoma of stomach....	1	0	1	1
Anterior gastrojejunostomy for carcinoma	1	0	1	0
Cholecystectomy and choledochostomy with T tube for acute pancreatitis and chole- lithiasis .....	3	1	3	0
Total.....	100	11	100	9

restricted to irreversible circulatory collapse, since it must then be reflected in the total mortality rate.

#### EXPERIMENTAL

To establish reliable controls, alternate patients were chosen to the number of 200. Since the value of the therapy could not be determined if given to patients who manifestly would not need it (e. g., those with hernias, hysterectomies or vaginal plastics), only patients with lesions of graver nature were chosen. In the control and the treated group there were equal numbers of patients for the various operative procedures (table 1). All operations were performed with the patient under spinal anesthesia.

19. Wiggers, C. J.: *Physiology in Health and Disease*, Philadelphia, Lea & Febiger, 1939, p. 742.



TABLE 2.—Data on Treated and Control Patients Subjected to Radical Mastectomy

Treated Group					Control Group				
Fifteen patients with carcinoma of the breast were given desoxycoorticosterone acetate and intravenous injections of 5 per cent dextrose in physiologic solution of sodium chloride before and after operation. There were no deaths. All the patients were women.					Fifteen control patients were given ordinary preoperative and postoperative intravenous injections of 5 per cent dextrose in physiologic solution of sodium chloride. There were no deaths. All the patients were women.				
Administration of Desoxycoorticosterone Acetate					Intravenous Administration of Dextrose-Saline Solution				
Age *	Days Pre-operative	Days Post-operative	Days in Hospital †	Complications	Age *	Days Pre-operative	Days Post-operative	Days in Hospital †	Complications
36	1	12	17	None	49	1	2	15	None
55‡	1	12	21	None	60‡	1	2	16	None
30	1	12	19	None	26	1	2	25	None
49	1	12	23	None	34	1	2	19	None
41	1	12	16	None	45	1	2	14	None
41	1	12	17	None	44	1	2	20	None
66	1	12	19	None	67	1	2	21	None
59‡	1	12	22	None	55‡	1	2	17	None
37	2	12	15	None	45	1	2	18	None
40	1	12	15	None	48	1	2	16	None
35	2	12	17	None	45	1	2	17	None
56	1	12	19	None	49	1	2	17	None
52	2	11	17	None	54	1	2	17	None
49	2	10	17	Pneumonia in the left lower lobe	46	1	2	18	None
39	1	12	18	None	43	1	2	18	None

\* Average age: treated group, 45.6; control group, 46.3 years.

† Average days in hospital: treated group, 17.9; control group, 17.5.

‡ Condition only fair.

TABLE 3.—Data on Treated and Control Patients Subjected to Gastrectomy for Carcinoma

Treated Group							Control Group						
Eighteen patients were given desoxycorticosterone acetate intramuscularly and 5 per cent dextrose in physiologic solution of sodium chloride intravenously before and after operation. Thirteen patients were only fair risks; 5 were good risks; 2 deaths occurred.							Eighteen control patients were given 5 per cent dextrose in physiologic solution of sodium chloride intravenously before and after operation. Thirteen patients were only fair risks; 5 were good risks; 1 death occurred.						
Age *	Sex	Administration of Desoxycorticosterone Acetate			Days in Hospital †	Complications	Age *	Sex	Intravenous Administration of Dextrose-Saline Solution			Days in Hospital †	Complications
		Days Pre-operative	Days Post-operative						Days Pre-operative	Days Post-operative			
59	F	2	12		18	None	63	F	1	3		18	None
71	M†	1	14		19	Pneumonia in the right lower lobe	77	F†	1	3		18	None
46	M§	2	14		20	None	51	M	2	3		18	Pneumonia in the left lower lobe
67	M†	2	14		17¶	Cerebral hemorrhage	59	M‡	2	3		17	None
48	M	2	14		19	None	69	M	1	3		16	None
62	M†	1	13		18	Bilateral broncho-pneumonia	71	M‡	2	3		15	None
58	M†	1	14		17	None	65	F†	1	3		18	None
60	F†	2	11		16	None	59	M§	2	2		18	None
60	M†	2	12		16	None	39	M†	2	3		17	None
42	M†	1	13		23	None	65	F†	1	2		20	None
43	M	2	14		21	None	43	M§	1	3		17	None
66	F†	2	7		11¶	Bilateral bronchopneumonia with cardiac decompensation	57	M§	1	4		5¶	Peritonitis
66	M†	2	13		23	None	71	F†	1	2		19	None
61	M†	2	13		15	None	64	M‡§	2	3		15	None
55	M†	1	14		21	None	51	F†	1	2		14	None
53	F¶	3	11		14	None	58	M‡§	1	2		14	None
44	M	1	13		16	None	44	M§	2	2		17	None
62	M†	1	13		15	None	55	F†	1	2		15	None

\* Average age: treated group, 57.5; control group, 58.9 years.

† Average days in hospital (not including patients who died): treated group, 18.1; control group, 16.8.

‡ Fair risk.

§ Ulcer found on pathologic study.

|| Sarcoma found on pathologic study.

¶ Patient died.

TABLE 4.—Data on Patients Subjected to Gastrectomy for Ulcer

Treated Group						Control Group					
Twenty patients were given desoxyeorticosterone acetate and 5 per cent dextrose in physiologic solution of sodium chloride before and after operation. There were 2 deaths.						Twenty control patients were given 5 per cent dextrose in physiologic solution of sodium chloride before and after operation. There were 3 deaths.					
Administration of Desoxyeorticosterone Acetate						Intravenous Administration of Dextrose-Saline Solution					
Age *	Sex	Days Pre-operative	Days Post-operative	Days in Hospital †	Complications	Age *	Sex	Days Pre-operative	Days Post-operative	Days in Hospital †	Complications
50	F	1	13	15	None	41	M	2	2	15	None
47	M	2	13	16	None	52	M	3	3	17	None
44	M	2	3	18	Pneumonia in the left lower lobe	25	M	2	5	16	None
46	M	1	16	18‡	Pulmonary embolism	63	M	1	3	4¶	Bronchopneumonia and cardiac decompensation
42	M	2	12	17	None	53	M§	1	3	14	None
31	F†	1	12	17	None	38	M‡	1	4	16	None
46	M‡	1	16	38	Pneumonia in the left lower lobe	68	F†	1	2	17	None
47	M‡	2	13	14	None	55	M‡	1	2	14	None
55	M	2	17	21	None	62	M§	1	3	15	None
50	M	3	3	6¶	Cerebral thrombosis with hemiplegia and cardiac decompensation	44	M	1	5	16¶	Pulmonary embolism
46	M	2	13	15	None	41	M	1	3	16	None
39	F	2	10	21	None	38	M	1	2	12	None
45	M	2	13	15	None	43	M§	1	3	16	None
37	M	3	13	21	None	54	M	2	2	18	None
36	M	2	10	15	None	43	M	1	3	16	None
33	F	2	10	16	None	44	M	1	3	16	None
30	M	2	11	16	None	33	M	2	3	16	None
55	M	2	10	20	None	46	M§	1	3	17	None
59	F	3	11	22	None	40	M	2	3	18	None
57	M‡	2	10	16	None	49	M†	2	2	17	None

\* Average age; treated group 45.7; control group 42.0.

\* Average age: treated group, 45.1; control group, 46.6 years.

† Average days in hospital (not including those who died): treated group, 18.5; control group, 15.8.

‡ Fair risk (4 patients in each group).

§ Carcinoma found on pathologic study (4 cases in control group).

¶ Patient died.

TABLE 5.—Data on Treated and Control Patients Subjected to Abdominoperineal Resection of the Rectum for Carcinoma

Treated Group						Control Group					
Eleven patients were given desoxycorticosterone acetate intramuscularly and 5 per cent dextrose in physiologic solution of sodium chloride intravenously before and after operation. There were 3 deaths.						Eleven control patients were given 5 per cent dextrose in physiologic solution of sodium chloride intravenously before and after operation. There was 1 death.					
Administration of Desoxycorticosterone Acetate						Intravenous Administration of Dextrose-Saline Solution					
Age *	Sex	Days Pre-operative	Days Post-operative	Days in Hospital †	Complications	Age *	Sex	Days Pre-operative	Days Post-operative	Days in Hospital †	Complications
62	M	2	13	38	None	40	M	1	2	37	None
65	M‡	1	14	30	None	63	F‡	1	2	18	None
55	F	1	12	26	None	52	M	1	2	18	None
28	F	1	14	34	None	42	F	2	2	31	None
64	F‡	3	13	60	Bilateral bronchopneumonia	81	F‡	2	3	30	None
60	M‡	2	14	36	None	66	F‡	2	3	31	None
45	F	1	12	35	None	71	M	2	2	37	None
56	F‡	3	7	10½	Cerebral hemorrhage and cardiac decompensation	61	M‡	1	3	24	Pneumonia in the left lower lobe
60	M‡	2	13	48	Pneumonia in the right lower lobe	35	F‡	2	2	42	None
63	F‡	2	13	49½	Pulmonary embolism	68	M‡	2	3	9½	Bilateral bronchopneumonia and cardiac decompensation
73	M‡	2	10	39	None	66	F‡	2	2	41	None

\* Average age: treated group, 59.1; control group, 60.4 years.

† Average days in hospital (not including patients who died): treated patients, 34.8; control patients, 31.2.

† Condition only fair.

**¶ Patient died.**

TABLE 6.—Data on Treated and Control Patients Subjected to Resection of the Colon for Carcinoma

Treated Group						Control Group					
Ten patients were given desoxycorticosterone acetate intramuscularly and 5 per cent dextrose in physiologic solution of sodium chloride intravenously before and after operation. There were 2 deaths.						Ten control patients were given 5 per cent dextrose in physiologic solution of sodium chloride. There was 1 death.					
Age *	Sex	Administration of Desoxycorticosterone Acetate		Days in Hospital †	Complications	Age *	Sex	Intravenous Administration of Dextrose-Saline Solution		Days in Hospital †	Complications
		Days Pre-operative	Days Post-operative					Days Pre-operative	Days Post-operative		
53	M†§	2	17	34	None	68	F†§	1	3	31	None
55	M‡	2	7	9	Peritonitis	55	F‡	1	2	43	None
66	F‡	2	14	50	None	52	F‡	2	3	39	None
64	M‡	1	3	4	Coronary occlusion and bilateral bronchopneumonia	53	F‡	1	3	20	None
59	F‡	1	14	43	Pneumonia in the right lower lobe	43	M‡	1	3	26	None
58	M‡	3	14	24	None	65	F‡	1	2	19	None
57	F‡	2	14	30	Fecal fistula	70	M‡	4	3	21	Bilateral bronchopneumonia
52	M	1	18	28	None	45	F	2	3	18	None
47	M†§	1	23	51	None	59	F†§	1	2	42	None
57	M‡	2	14	10	None	43	M‡	1	3	25	None

\* Average age: treated group, 57.3; control group, 55.3 years.

† Average days in hospital (not including patients who died): treated group, 34.8; control group, 29.2.

‡ Fair risk.

§ Primary eecostomy with subsequent resection.

|| Exteriorization.

‡ Patient died.

TABLE 7.—Data on Treated and Control Patients Subjected to Various Operative Procedures

Treated Group					Control Group					
Desoxycholesterone acetate was given twice daily intramuscularly with intravenous injections twice daily of 5 per cent dextrose in physiologic solution of sodium chloride before and after operation.					Twice daily 5 per cent dextrose in physiologic solution of sodium chloride was given intravenously before and after operation.					
Age	Sex	Desoxycholesterone Acetate			Complications	Intravenous Administration of Dextrose-Saline Solution			Complications	
		Days Pre-operative	Days Post-operative	Days in Hospital		Days Pre-operative	Days Post-operative	Days in Hospital		
67	M*	2	10	18	Cholecystenterostomy for Carcinoma of the Pancreas	58	F*	2	3	None
48	M*	2	13	15		60	F*	2	3	Pulmonary embolism
72	M*	2	11	22	Excision of Retroperitoneal Sarcoma	37	F*	1	2	None
55	F*	3	3	9†	Thoracotomy for Excision of Sarcoma of the Thoracic Cavity	16	M*	1	1	Cardiac decompensation
53	F*	1	16	22	Previous Cholecystostomy for Acute Pancreatitis, Secondary Cholecystectomy and Cholecholestomy with T Tube for Lithiasis	46	F*	2	3	None
56	M*	1	15	30	Thoracoplasty for Pulmonary Tuberculosis	32	M*	1	2	None
62	M*	2	12	15	Nephrectomy for Carcinoma	18	F*	1	2	None
70	F†	1	13	19	Anterior Gastrojejunostomy for Inoperable Carcinoma with Obstruction	71	F†	1	3	None
62	F*	1	14	17	Laparotomy for Carcinoma of the Stomach (Found Inoperable at Operation)	66	M*	1	3	Pulmonary embolism
70	F*	3	14	24	Ileosigmoidostomy for Carcinoma	61	F*	1	3	None
58	M*	1	13	23	Colostomy for Carcinoma	42	F*	1	3	None
50	M*	2	13	27		10	M*	2	2	None
54	F*	2	14	27	Pneumonia in the right lower lobe	60	F*	2	1	None
59	F*	1	14	46	Obstructive Resection for Carcinoma	68	M*	1	3	None
46	F*	3	13	21	Splenectomy	64	F*	1	3	None
63	F*	1	13	29	One Stage Resection for Regional Enteritis	62	F*	1	3	Bilateral broncho-
37	M‡	1	13	26	Fecal fistula	29	F‡	1	3	pneumonia
30	M*	3	7	10†	Pneumonia	18	F*	1	3	Fecal fistula
23	M‡	1	12	53	None	26	M‡	1	3	None
25	M	1	13	18	None	20	F	1	3	None

\* Fair condition.

† Poor condition.

‡ Patient died.

§ Exteriorization of the anastomosis.

TABLE 8.—Data on Treated and Control Patients Who Were in Some Degree of Shock at the Time of Operation

Treated Group					Control Group				
Five cubic centimeters of adrenal cortical extract was given four times a day for two days; then 1 ampule of desoxycorticosterone acetate twice daily for four days and daily for eight days. Five per cent dextrose in physiologic solution of sodium chloride also was given intravenously.					Five per cent dextrose in physiologic solution of sodium chloride only was given.				
Age	Sex	Days of Post-operative Treatment	Days in Hospital	Complications	Age	Sex	Days of Post-operative Treatment	Days in Hospital	Complications
Cholecystectomy and Choledochostomy with T Tube Drainage and Drainage of the Pancreas for Acute Pancreatitis									
31	F*	14	25	None	42	M*	5	25	None
53	F†	14	18	None	40	M†	4	23	None
53	M†	3	3‡	Peritonitis	63	F†	3	19	None
Purse String Suture for Acute Perforated Gastroduodenal Ulcer									
47	M*	14	15	None	25	M*	3	18	None
50	M†	14	18	None	77	M†	3	16	None
Amputation of Leg (Midhigh)									
8	M‡§	14	72	None	69	M¶	2	45	None

\* Fair condition.

† Poor condition.

‡ Patient died.

§ Patient had compound fracture of both legs with gangrene of the right leg.

|| Debilitated patient with diabetes and gangrene of the right leg.

Twelve of the 200 patients (6 treated and 6 untreated) had conditions acute in nature and were considered in shock at the time of operation. Four had perforated pyloric ulcers; 6 had acute hemorrhagic pancreatitis, and 2 had amputations of the lower extremity—the one, a young boy of 8 years who suffered from severe shock following compound fracture of both legs, and the other, an old debilitated patient with diabetes and gangrene. The treated patients with acute conditions were given 5 cc. of adrenal cortical extract intramuscularly every six hours for the first forty-eight and then 5 mg. of desoxycorticosterone acetate twice daily for four days and once daily subsequently for ten to fourteen days. All received 1,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride twice daily for the first four days. The other 94 patients in the treated group (there was ample opportunity to prepare them preoperatively since they were being operated on for chronic lesions) all were given 5 mg. of desoxycorticosterone acetate twice daily for anywhere from one to four days before operation and the same dose twice daily for the first four days postoperatively; after this only one injection a day was given up to the fourteenth day after operation. All of them received intravenous injections of 1,000 cc. of 5 per cent dextrose and saline solution twice a day before operation and for the first four days after operation. The 94 control patients were treated in exactly the same manner except that they received no desoxycorticosterone acetate or adrenal cortical extract. Transfusions and supplementary vitamin therapy were given to patients in both groups whenever it was believed the indication warranted it.

### RESULTS

The effect of the therapy on the operation and the convalescence and the result in the control cases are given in tables 2 to 8.

### COMMENT

From a study of the 200 cases selected for this experiment, it can be seen that the value of any addition to the therapy ordinarily employed should be reflected in the mortality rate. If desoxycorticosterone acetate could do anything to prevent death, these cases would offer it a fine opportunity to demonstrate its usefulness. Among the 100 treated patients, there was a mortality rate of 11 per cent, and among the control patients, there was a mortality rate of 9 per cent. Even if reversed, this difference of percentages has absolutely no significance according to the method of calculating the significance of differences in percentages suggested by Fisher.<sup>20</sup> Previous workers in this field have, however, attached significance to the results obtained by the use of adrenal cortical extract. Wilson, MacGregor and Stewart<sup>1a</sup> expressed the opinion that adrenal cortical extract may have a favorable influence in the treatment of shock from burns and scalds. They gave the protocols of 13 cases, in only 3 of which adrenal cortical extract was given. Two of the 3 patients recovered, 1 supposedly with a dramatic effect as a

20. Fisher, R. A.: *Statistical Methods for Research Workers*, ed. 6, Edinburgh, Oliver & Boyd, 1936, p. 47.



result of the use of extract of adrenal cortex. The authors mentioned in the text that their personal experience was limited to 3 additional cases, in 2 of which adrenal cortical extract was without obvious action. Their impressions, therefore, were gained from 6 cases. Since 3 of the patients died, it was obviously of no value in this small group of cases. Reed<sup>1c</sup> gave adrenal cortical extract to a series of over 50 operative patients. He reported 8 cases in detail. Two patients were operated on for pelvic inflammatory disease; 2, for acute appendicitis; 1, for chronic appendicitis; 1, for cholecystitis; 1, for ectopic pregnancy, and 1, for thyroid adenoma. Without any controls, Reed gathered the clinical impression that the use of adrenal cortical extract either prevented shock or, when shock occurred, was of definite value in helping the patient combat it. Perla<sup>1b</sup> gave desoxycorticosterone acetate and solution of sodium chloride to 12 patients who were considered poor risks; their cases were reported because no shock developed in them and they all recovered. Discussing experiences at a casualty-clearing station in a small military hospital where the major problem was the treatment of 500 of the more seriously wounded evacuated from Flanders, Brown, Dennison, Ross and Divine<sup>18a</sup> described the routine treatment which they gave in 20 cases of extensive second and third degree burns. All of their patients exhibited secondary shock or toxemia on admission, and some had suffered from immersion in the sea. Besides their routine burn treatment, they used desoxycorticosterone acetate also. They felt that desoxycorticosterone acetate proved its value in many of these cases. Among the 20 patients treated there was a mortality rate of 25 per cent. However, there were no control observations, and the number of observations was limited to 20 as has already been mentioned. Besser<sup>1d</sup> attempted a controlled experiment and reported on the value of desoxycorticosterone acetate in the prevention of operative shock in 72 cases. He pointed out the difficulty of determining the value of a therapeutic measure in the prevention of shock associated with operative procedures, and he arbitrarily used a blood pressure of 80 systolic and 60 diastolic as the level below which the onset of shock was indicated. He pointed out also that the use of methods to determine hemoconcentration was not satisfactory under the conditions of the experiment, since many other circumstances besides shock itself could contribute to changes in hemoconcentration. As controls, he used 68 untreated patients, and he concluded (clinical impression) that desoxycorticosterone was of little value in preventing shock. Unfortunately, no information was given regarding the mortality rate in the treated and the untreated group.

If it can be assumed that all deaths in the treated and control groups in our experiment were due to shock alone, then desoxycorticosterone acetate manifestly had no value in preventing shock since there were more

deaths in the treated series. To show that the treatment had any value, it would be necessary to find a lower mortality rate in the treated than in the control group. To be statistically significant, the difference in mortality rate, it can be shown, would have to be greater than 6 per cent. By this is meant that if the control group mortality rate of 100 patients is 9 per cent, then in the treated group of 100 patients the mortality rate must be less than 3 per cent to establish the probability that the difference between the two was other than an accidental occurrence.

It is likely that other factors besides shock contributed to the deaths in both groups. It therefore becomes evident that the mortality rate in the treated group would have to be even less than 3 per cent to be significant, if the trial is limited to 200 cases. Since, however, there was no reduction in the mortality rate in the treated group, it may be concluded that there is no evidence in this experiment that desoxycorticosterone acetate can prevent or favorably influence postoperative shock as reflected by the mortality rate. It seems also that enthusiastic reports of its value in other instances of its use in human beings are not supported by data.

#### SUMMARY

Two hundred patients operated on for conditions such that shock might reasonably be expected to develop during or after the operation were studied in this experiment. One hundred alternately chosen were treated with desoxycorticosterone acetate and parenteral solution of sodium chloride. The mortality rate in the treated and control groups was used as the criterion of the effectiveness of the therapy, the term "shock" being assumed to denote an irreversible state of circulatory failure.

There was no evidence that the therapy prevented or favorably influenced shock.

# PRACTICAL METHOD OF PREDICTING THE GROWTH OF THE FEMUR AND TIBIA IN THE CHILD

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Inequality in the length of legs is a problem which is fundamentally important to the orthopedic surgeon. Before the development of our method of leg lengthening,<sup>1</sup> the standard treatment prescribed for patients with shortening of one of the lower extremities was the application of a lift to the sole of the shoe.<sup>2</sup> The success of the method employed by us aroused new interest on the part of orthopedic surgeons in many clinics throughout the country. Later, the original technic was modified in the hope that the operation could be simplified and freed from complications.<sup>3</sup> Despite these efforts, the operation remains today one of considerable magnitude and one to be performed only in a selected group of cases. It should never be attempted by the inexperienced surgeon who lacks detailed and anatomic knowledge of every step of the operation and the postoperative care.

After considerable experience with the procedures for lengthening the femur and lengthening the tibia and the fibula, we have reached the opinion that while the main purpose of our method is of limited value, a number of valuable by-products have been developed. The approaches

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1. This method was developed at the Shriners' Hospital for Crippled Children, St. Louis, by Drs. L. C. Abbott and C. H. Crego Jr. and at the University of California Medical School by Drs. L. C. Abbott and John B. deC. M. Saunders..

2. Abbott, L. C.: The Operative Lengthening of the Tibia and Fibula, *J. Bone & Joint Surg.* **9**:128 (Jan.) 1927.

3. Abbott, L. C., and Saunders, J. B. deC. M.: The Operative Lengthening of the Tibia and Fibula: A Preliminary Report on the Further Development of the Principles and the Technique, *Ann. Surg.* **110**:961 (Dec.) 1939.

which have been devised as a result of the many anatomic dissections are useful in other operations on the lower extremities. Furthermore, the dissections have accurately shown the points of fixation by fascia of the nerves of the extremity. For example, the common peroneal and posterior tibial nerves are fixed respectively at the neck of the fibula and the upper border of the soleus muscle. Freeing these nerves from their points of fixation together with flexion of the knee produces sufficient slackening to permit lengthening of the tibia and the fibula  $1\frac{1}{2}$  inches (3.8 cm.) without undue tension on the substances of the nerves. This information is useful to the surgeon in suturing the nerves when there has been a considerable loss of substance. The apparatus which has been devised with a two, three and four pin fixation for the control of the fragments after osteotomy has led to the use of similar traction appliances for the treatment of complicated fractures. In some fractures, the use of these appliances has obviated the necessity for open reduction. Experience with leg-lengthening procedures gives further knowledge regarding the formation of callus and the effects of stress and strain on early formation of bone.

As an alternative procedure to lengthening the short leg, shortening of the sound leg is now commonly employed. It is the most accurate method for the equalization of the length of the legs. In considering its use, however, it is well to remember that in the growing child there may be a number of factors producing discrepancy in length which require a period of observation and study. Further, the rate of growth of the shortened leg may be altered considerably by changes in the circulation as a result of operative procedures or continued activity of disease with the involvement of epiphysial cartilage plates. In our opinion, therefore, the operation of leg shortening should be reserved for use in cases in which growth has been completed.

The operation of leg shortening has been performed with many types of osteotomy. If the operation is ever indicated in young children, simple transverse division of the bone, overlapping of the fragments to the desired amount and then fixation by horizontal pins seems to be satisfactory.<sup>4</sup> In older children and adults, a more carefully planned osteotomy with mortising of the fragments is essential. The underlying principles are the same in any of the operative procedures, namely, restoration of alinement and complete fixation of the fragments until union takes place.

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4. White, J. W., and Warner, W. P.: Experiences with Metaphyseal Growth Arrests, *South. M. J.* **31**:411 (April) 1938.

The operation has been performed in the upper, middle and lower thirds of the femur. We have had success with the use of all three sites, but union has taken place with greater rapidity when the osteotomy has been performed through cancellous bone at either the upper or the lower third. The least disturbance to the function of the quadriceps muscle group and to the knee joint occurs when osteotomy is done through the upper third. A special type of osteotomy together with a description of the anatomic approach which we have used in this region will be discussed in a later article.

In growing children, the most useful method for equalization of leg length is the epiphysial arrest advocated by Phemister.<sup>5</sup> This operation is simple, its only drawback being the permanent shortening of stature. This procedure used alone or with operations for lengthening of the leg demands an accurate method of estimating the future rate of growth, the ultimate length of the extremities and the final height.

In this paper we shall describe a method for the prediction of future growth of the femur and the tibia which we believe to be the most reliable of all methods of which we have knowledge. Before describing it in detail, we shall review in brief the work of others with relation to this problem.

The studies of Phemister and Hatcher have been of great importance in emphasizing the value of epiphysial arrest in the treatment of inequality in the leg length of growing children. To make this operation of practical value, they devised a method of determining the average growth of the lower limbs at various ages. These authors used Baldwin's data, which represented average measurements for the standing and the sitting height of a large group of children at various ages. The growth in the length of the legs at each age was determined by subtraction of the average leg length at each age from the average length of the legs at full growth.<sup>6</sup> Digby's figures for the percentage of growth from the individual epiphyses of the femur and the tibia were converted into percentages of growth for the entire lower extremity.<sup>7</sup> These percentages were then multiplied by the expected growth of the leg in order to give the exact amount of growth contributed by each epiphysis. An attempt was made to individualize the predictions of growth by using the stature and the leg length of the parents.

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5. Phemister, D. B.: Operative Arrestment of Longitudinal Growth of Bones in the Treatment of Deformities, *J. Bone & Joint Surg.* **15**:1 (Jan.) 1933.

6. Baldwin, B. T.: Physical Growth of Children from Birth to Maturity, *Studies in Child Welfare*, Iowa City, University of Iowa, 1921, vol. 1, no. 1.

7. Digby, K. H.: The Measurement of Diaphyseal Growth in Proximal and Distal Directions, *J. Anat. & Physiol.* **50**:187, 1915-1916.

We believe, however, that there are five valid objections to this method of estimating the possible growth from the individual epiphyses of the femur and the tibia. The same criticisms apply to similar methods used by Wilson and Thompson<sup>8</sup> and White.<sup>4</sup>

1. Average figures for the length of legs cannot be applied because of the wide variations in the final leg length of individual children. Meredith's figures for leg length at completed growth show that in boys the measurements ranged from 27.8 to 37.3 inches (70.61 to 94.74 cm.), a difference of 9½ inches (24.13 cm.) (fig. 1). In girls, the range was from 26.6 to 34.1 inches (67.56 to 86.61 cm.), a variation of 7½ inches

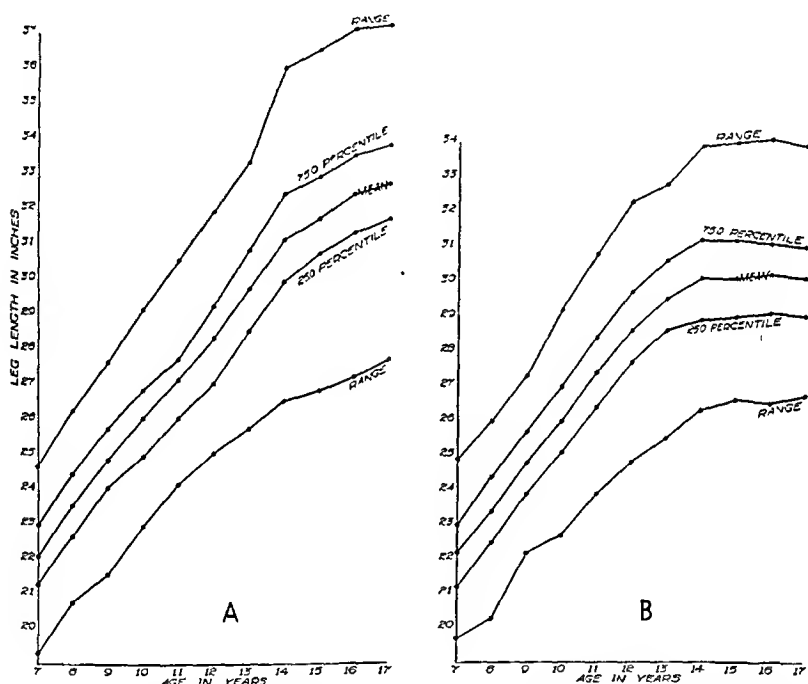


Fig. 1.—Leg lengths as drawn from data of Meredith, i. e., stature minus stem length. A, boys; B, girls.

(19.05 cm.).<sup>9</sup> In addition, Bach<sup>10</sup> found that in adults of various heights there is so much disparity in the proportions of the length of

8. Wilson, P. D., and Thompson, T. C.: A Clinical Consideration of the Methods of Equalizing Leg Length, *Ann. Surg.* **110**:992 (Dec.) 1939.

9. Meredith, H. B.: Length of Head and Neck, Trunk and Lower Extremities on Iowa City Children Aged Seven to Seventeen Years, *Child Development* **10**: 129 (June) 1939.

10. Bach: Veränderungen der Oberschenkelänge und Unterschenkelänge mit steigender Körpergröße, in Martin, R.: *Lehrbuch der Anthropologie*, ed. 2, Jena, Gustav Fischer, 1928, vol. 1, pp. 416-417.

the limbs to the total stature, that many persons of medium height may have legs as long as taller persons (fig. 2).

2. Leg length is an unsatisfactory measurement for several reasons. It is usually obtained by subtracting the sitting height from the standing height and for that reason includes structures other than the femur and the tibia. From this measurement, it is not possible to study the growth of the normal bones and, even more important, to determine the actual mechanism producing abnormal growth in any given case. On the other hand, teleroentgenograms taken with the tube at a distance of 6 feet (183 cm.) give a permanent record of the length of the femur and the tibia

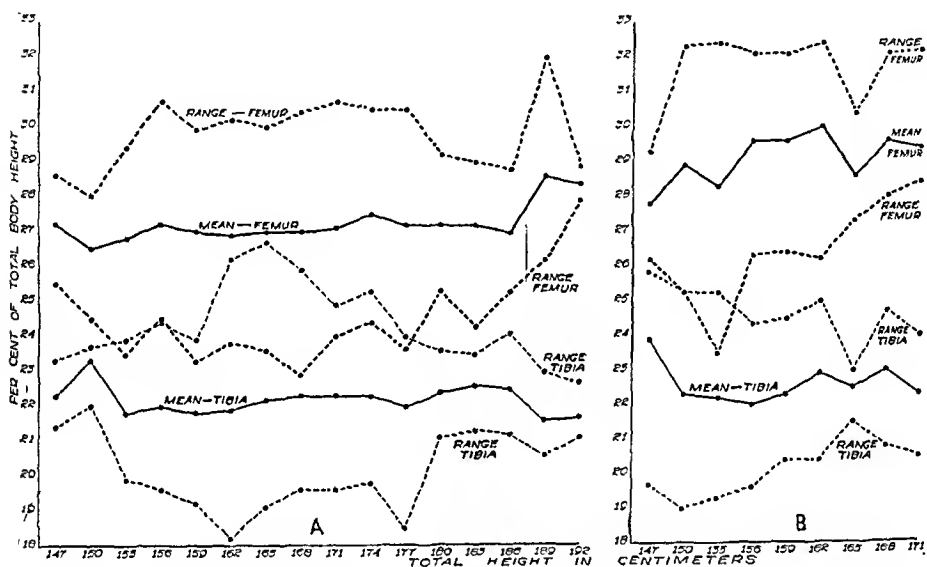


Fig. 2.—Leg length as percentage of total body height as drawn from data of Bach. A, men; B, women.

with only a small degree of distortion. This distortion is almost constant and may therefore be virtually disregarded in most instances.

Another method, slit scanography, devised by Millwee,<sup>11</sup> is even more accurate. Recently, we have been using a modification of this method which is now in process of further development. The tube port is covered by a lead mask with a transverse slit 2 mm. wide. During a lengthened exposure, the tube is slowly moved the length of the bone to be measured at a rate of about 36 inches (91 cm.) per ten seconds. This results in films of good quality with the exact lengths of the bones. The distance of the tube from the limb may be as short as desired.

11. Millwee, R. H.: Slit Scanography, *Radiology* 28:483 (April) 1937.

3. There is no allowance for the frequent variations in the sexual and the skeletal development of children of the same age. This, as will be shown later, may lead to serious errors in the prediction of the future growth of a child.

4. The use of the parents' measurements is not reliable in determining the future growth of the child. Baldwin<sup>6</sup> and Wallis<sup>12</sup> have shown in their studies that calculations of the final growth of the child based on its measurements with relation to those of its group are more accurate than those based on the measurements of its parents. It seems obvious that with parents of varying height, it would be impossible to guess which parent the child might resemble in final stature.

5. Digby's figures, as used by Phemister and Wilson, presuppose that the femur and the tibia grow at the same relative rate during the

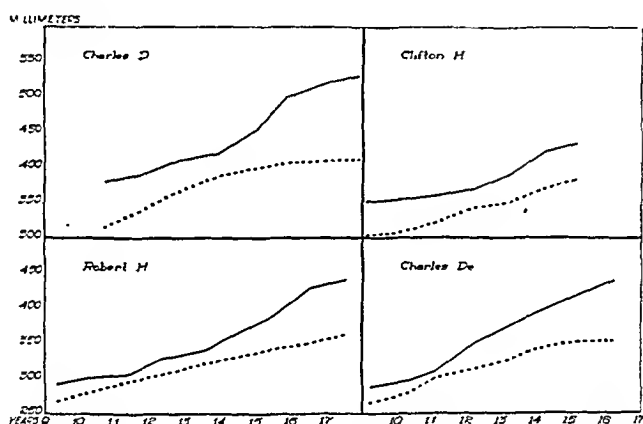


Fig. 3.—Growth curves of the upper and the lower parts of the leg as drawn from data of Davenport. The solid line represents the upper part of the leg, and the broken line, the lower part. All the patients were white boys except Clifton H., who was a mixture of Negro and white.

entire period of growth. This, however, is not true, as was shown by Schultz,<sup>13</sup> Scherz<sup>14</sup> and Davenport.<sup>15</sup> Davenport demonstrated that

12. Wallis, R. S.: *How Children Grow: An Anthropometric Study of Private School Children from Two to Eight Years of Age*, Studies in Child Welfare, Iowa City, University of Iowa, 1931, vol. 5, no. 1.

13. Schultz, A. H.: *Fetal Growth of Man and Other Primates*, Quart. Rev. Biol. **1**:465 (Oct.) 1926.

14. Scherz: *Schaffhauser Kinder*, in Martin, R.: *Lehrbuch der Anthropologie*, ed. 2, Jena, Gustav Fischer, 1928, p. 414.

15. Davenport, C. B.: *The Crural Index*, Am. J. Phys. Anthropol. **17**:333 (Jan.-March) 1933.



there is a change in the relative rates of growth of these bones in boys (fig. 3). The femur, longer than the tibia at birth, grows slowly in the juvenile period. At the age of 11 or 12 years, just before puberty, it begins to grow more rapidly. In contrast, the tibia grows uniformly, though at a faster rate than the femur during the juvenile period until about the age of 13 or 14, when its growth is damped off just at the time the femur is beginning to grow more rapidly. Thus, the tibia obtains its final growth before the femur. The results of the work of Schwerz (fig. 4) agreed fairly well with those of Davenport, though the study was based on average measurements, which tend to mask the findings shown by a study of an individual case like Davenport's. Hatcher's curves of growth for the femur and the tibia show no change in the relative rates of growth of these bones.<sup>16</sup> However, these curves also are based on average measurements.

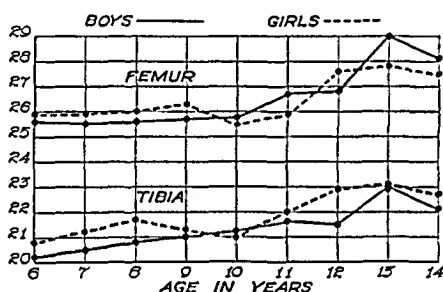


Fig. 4.—Femur and tibia as percentage of stature as drawn from data of Schwerz. The solid line represents boys, and the broken line, girls.

#### METHOD

From an extensive review of the anthropologic literature on the growth of children, we have developed a method which to a great extent overcomes the objections just mentioned. While we believe that it is more accurate than any now in use, we realize that it may be improved on as more detailed data on the growth of children is obtained. This method is based on two findings: 1. The final stature of a child may be predicted accurately by the use of the percentile method. This accuracy is increased if the bone maturation age of the child is considered. 2. The relative proportions of the length of the femur and the tibia to stature in a person are maintained with only small age variations throughout the adolescent period. Therefore, it is a matter of simple arithmetic to predict the final length of the femur and the tibia in any child by taking the present proportions of these bones to stature, adding small changes according to age and multiplying these proportions by the predicted final height.

16. Hatcher: Growth Increment Curve for the Femur and Tibia, in Campbell, W. C.: *Operative Orthopedics*, St. Louis, C. V. Mosby Company, 1939, p. 954.

Our method of determining the expected growth of the normal femur and tibia is as follows:

1. The child's height is measured as it stands on the normal leg with the pelvis level.<sup>17</sup>

2. The age is recorded in years and months. This is checked against the skeletal maturation age obtained from Todd's Atlas of Skeletal Maturation

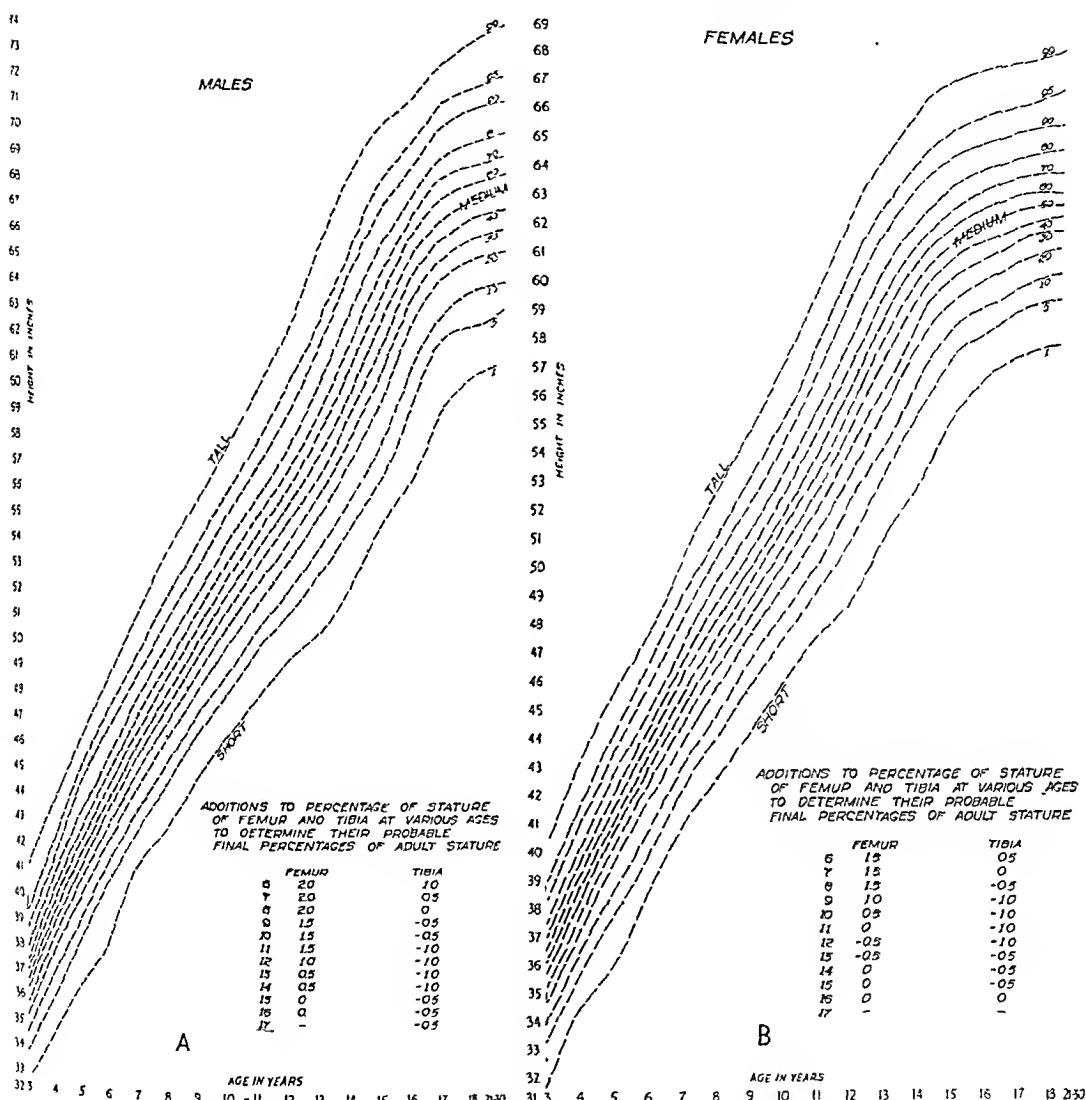


Fig. 5.—Curves of percentile distribution of height constructed from the tables for percentile distribution of stature given by the White House Conference on Child Health and Protection in 1932. The subtables included in the charts were compiled from different data.

17. Measurement of the total height is taken with the patient standing on the normal leg. Blocks are placed under the short leg until the pelvis is level. The buttocks, the shoulders and the head should touch the wall.

(Hand).<sup>18</sup> If the skeletal maturation is more than six months advanced or retarded from the chronologic age, the skeletal age should be substituted for the chronologic age in all further calculations.

3. From the sex, the height and the corrected age, the person is placed in his or her percentile position of the percentile chart (fig. 5).<sup>19</sup> By following up the chart between the parallel percentile curves to the completion of growth, the expected final stature of the person is obtained. In boys, growth is complete at the age of 18½ years; in girls, at the age of 16½.

4. The lengths of the femur and the tibia are measured from teleroentgenograms or slit scanograms.<sup>20</sup>

5. The present percentage of the normal femur to the stature is obtained by dividing its length by the present height and multiplying by 100. The same calculation is carried out for the tibia.

6. To the present percentages of the normal femur and tibia to stature, as calculated under 5, are added the amounts, either positive or negative (as given in the subtable in figure 5), according to the sex, the corrected age and the bone. This gives the estimated adult percentages of these bones to stature.

7. These percentages are then multiplied by the predicted stature to give the expected final length of each bone.

8. By subtracting the present length of the normal femur from the expected final length of the normal femur, the expected growth of this bone is obtained. The expected growth of the normal tibia is obtained in the same manner.

9. Growth from the distal part of the femur = expected femoral growth  $\times$  70 per cent

Growth from the proximal part of the tibia = expected tibial growth  $\times$  55 per cent

Growth from the distal part of the tibia = expected tibial growth  $\times$  45 per cent

The following example will serve to clarify the various steps in predicting the growth of the normal femur and tibia. Suppose the patient to be a girl.

1. Height = 53 inches (160.02 cm.)

2. Age = 9 years

Bone maturation age = 10 years.

18. The skeletal maturation age may be determined by comparison of an anteroposterior roentgenogram of the hand with standards in Todd, T. W.: *Atlas of Skeletal Maturation (Hand)*, St. Louis, C. V. Mosby Company, 1937. The skeletal maturation age may be determined also from the knee, but, unfortunately, Todd's standards for the knee are not printed in atlas form. For this reason, it is simpler to determine the skeletal maturation age from the hand.

19. The curves of percentile distribution of height (fig. 5) were constructed by us from the tables for percentile distribution of stature given by the White House Conference on Child Health and Protection in 1932.<sup>21</sup>

20. The lengths of the femur and the tibia are to be determined from roentgenograms of the femur and the tibia taken at a distance of 6 feet (183 cm.), the tube to be centered in the approximate middle of each bone or from scanograms. From these films the measurements are made as follows: femur, a straight line from the tip of the femoral head to the medial lip of the internal femoral condyle at the joint line; tibia, a straight line from the medial lip of the internal tibial condyle at the joint line to the tip of the internal malleolus.

3. The expected total stature = 64 inches (162.56 cm.)
4. Length of femur = 14.8 inches (35.56 cm.)  
Length of tibia = 12.5 inches (31.75 cm.)
5. Femoral percentage of stature =  $\frac{14.8 \text{ inches}}{53 \text{ inches}} \times 100 = 28 \text{ per cent}$   
Tibial percentage of stature =  $\frac{12.5 \text{ inches}}{53 \text{ inches}} \times 100 = 23.5 \text{ per cent}$
6. Femoral percentage of adult stature =  $28 + 0.5 = 28.5 \text{ per cent}$   
Tibial percentage of adult stature =  $23.5 + (-1.0) = 22.5 \text{ per cent}$
7. Final length of femur =  $28.5 \text{ per cent} \times 64 = 18.2 \text{ inches (46.23 cm.)}$   
Final length of tibia =  $22.5 \text{ per cent} \times 64 = 14.4 \text{ inches (36.58 cm.)}$
8. Expected growth of femur =  $18.2 - 14.8 = 3.4 \text{ inches (8.64 cm.)}$   
Expected growth of tibia =  $14.4 - 12.5 = 1.9 \text{ inches (4.83 cm.)}$
9. Growth distal femur =  $3.4 \times 70 \text{ per cent} = 2.4 \text{ inches (6.1 cm.)}$   
Growth proximal tibia =  $1.9 \times 55 \text{ per cent} = 1.05 \text{ inches (2.67 cm.)}$   
Growth distal tibia =  $1.9 \times 45 \text{ per cent} = 0.85 \text{ inches (2.16 cm.)}$

#### PREDICTION OF THE FINAL HEIGHT OF THE INDIVIDUAL CHILD

The accuracy of our predictions rests on the exactness with which height may be predicted by the percentile method. This method has long been used because numerous studies have shown that in a group of children, a given child tends to maintain his rank in stature from one age to another. In 1921, Baldwin<sup>6</sup> followed the growth in height of a small series of boys and girls representing similar stock. When the individual curves were plotted, he found that for each sex the curves of growth assumed a railroad appearance, each child maintaining his or her relative position from the ages of 6 to 17 years. There was a crossing of curves because girls have an earlier acceleration and an earlier cessation of growth than boys. From his data, Baldwin concluded that the height at the age of 15 or 16 years could be predicted within 3 or 4 cm. if the height were known at the age of 9 or 10 years. When Baldwin's children were plotted in a percentile manner, they stayed rather closely within their percentile range. In 1922, Porter found that the chances were 3 to 1 that no boy would vary as much as 14 percentile grades between the ages of 6 and 13 years. We have constructed the curves we use from the tables for percentile distribution of stature published in 1932 by the Committee on Growth and Development of the White House Conference on Child Health and Protection (fig. 5).<sup>21</sup> The 1 percentile grade is the stature of the shortest 1 per

21. Growth and Development of the Child: I. General Considerations, Report of the Committee on Growth and Development, Section 1, Medical Service, White House Conference on Child Health and Protection, New York, Century Company, 1932, pp. 93-108; Percentile tables, pp. 98-101; II. Anatomy and Physiology, *ibid.*, 1933, pp. 55-74; IV. Appraisalment of the Child, *ibid.*, 1932, pp. 258-278.

cent at each age; the 50 percentile grade, the stature of the persons in the middle group at each age; the 99 percentile grade, the stature of the tallest 1 per cent, and so on. To determine whether height could be predicted accurately enough for our purposes by the use of these curves, we reviewed the measurements of a group of children who had been followed to full growth. These children represented an average group of varying nationalities. The state of health varied, but none of the children was severely ill. A prediction of final height was made from each measurement taken during the growth period by following up between the parallel curves. These predictions were then compared to the actual final stature. In this manner, errors in the prediction of height for each age were readily found. Unfortunately, the children were not measured at sufficiently regular intervals to allow the calculations of the average error in the prediction of final height in each case.

In 33 girls (tables 1 and 2), the largest errors in the prediction of height in 75 per cent of the cases were less than 1.8 inches (4.58 cm.). In 12 boys (table 3), the largest errors in 75 per cent of the cases were less than 2½ inches (6.35 cm.). It must be remembered that these figures were based on the selection of the greatest discrepancy in each case. In all of the cases most of the errors were smaller. When we averaged our data, admittedly incomplete, the average error in the prediction of total stature was 1 inch (2.5 cm.), and in 90 per cent of the cases, the average error was under 2 inches (5.08 cm.). As the tibia and the femur each compose only about one fourth of the total stature, the error in the prediction of the length of these two bones would be one fourth of this amount. There is evidence that even these errors may be reduced by substitution of the bone maturation age for the chronologic age. Meredith found that there is often considerable variation in the percentile standing of children after the period of adolescence.<sup>22</sup> This is caused by differences in the degree of sexual maturation. For example, given 2 children of the same sex, height and actual age, the one with the most advanced sexual development will always become the shorter adult.<sup>22a</sup> Todd showed clearly that sexual maturation is closely correlated with skeletal maturation. He found that regardless of their chronologic age, girls began menstruation at an average skeletal maturation of 13½ to 14 years.<sup>23</sup> This age is the average age of menstruation for many large groups of girls.

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22. Meredith, H. B.: Stature of Massachusetts Children of North European and Italian Ancestry, *Am. J. Phys. Anthropol.* 24:301 (Jan.-March) 1939.

22a. Wilson and Thompson.<sup>8</sup> Meredith.<sup>22</sup>

23. Todd, T. W.: Growth and Development of the Skeleton, in Preliminary Report of the Committee on Growth and Development, White House Conference on Child Health and Protection, 1930, Sect. 1, Medical Service, New York, Century Company, 1930, p. C1. The Anatomical Features of Epiphyseal Union, *Child Development* 1:186 (Sept.) 1930.

TABLE 1.—Errors in Height Prediction of Girls with Theoretic Correction of Chronologic Age of Menstruation to Thirteen and a Half Years

Patient	Final Age	5 Yr.	6 Yr.*	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	13 Yr.	14 Yr.	15 Yr.	Maxi- mum Error	Age at Which Menstruation Began	Comment
1	18 yr., 9 mo.	..	..	..	..	+1.8 -1.0	+2.2 -0.3	..	+2.8 +0.6	+2.4 +0.4	+2.0 +0.4	....	+2.8 -1.0	12 yr.	
2	17 yr., 4 mo.	..	..	..	..	..	+4.3 +2.0	+5.2 +2.3	..	+4.2 +1.5	....	+1.8 +1.3	+5.2 +2.2	12 yr.	Latin
3	18 yr.	..	+2.1 -2.4	+1.9 -1.6	..	+2.1 -0.9	+2.5 -0.8	+2.7 -0.6	+2.5 0	+1.7 -0.3	+1.0 -0.4	+1.1 +0.1	+2.7 -2.4	13 yr.	
4	17 yr.	..	..	..	..	+1.0 -1.5	0 -1.8	+1.8 +0.1	+1.8 +0.2	+1.8 +0.2	+1.3 +0.6	....	+1.8 -1.8	12 yr., 5 mo.	
5	16 yr., 10 mo.	..	..	..	+3.5 +1.4	..	..	..	+2.0 0	+2.3 +1.1	+1.9 +1.2	+1.3 +1.0	+3.5 +1.4	12 yr., 7 mo.	
6	19 yr.	..	..	..	..	+0.5 -1.0	+0.7 -0.8	+1.3 -0.3	..	+2.0 +1.2	....	+0.7 +0.3	+2.0 +1.2	12 yr., 10 mo.	
7	19 yr.	..	..	..	..	..	..	..	+1.2 +0.5	....	+0.7 -0.1	+0.5 +0.3	+1.2 +0.5	12 yr., 11 mo.	Rheumatic fever at 11 years of age
8	17 yr., 7 mo.	..	..	..	..	..	-0.6 -1.5	+0.6 -0.5	..	..	+0.6 +0.3	+0.6 +0.3	+0.6 -1.5	13 yr.	
9	17 yr.	..	..	..	-1.1 -2.0	..	..	..	..	+0.8 -0.2	....	+0.8 +0.2	-1.1 -2.0	13 yr.	Congenital syphilis
10	16 yr., 9 mo.	..	..	..	..	..	..	-1.0 0	0 +0.8	-0.5 +0.1	+0.4 +1.0	+1.0 +1.3	+1.0 +1.3	14 yr.	
11	17 yr., 8 mo.	..	..	..	..	..	..	-0.5 +1.0	-1.6 -0.9	..	....	-0.8 -0.3	-1.6 +1.0	14 yr.	
12	17 yr.	..	-0.2 +1.5	+0.2 +1.5	..	0 +1.5	-0.2 +0.8	-1.7 +0.4	-1.8 0	-1.8 -0.5	-1.1 0	-0.7 0	-1.8 +1.5	14 yr., 3 mo.	
13	17 yr., 11 mo.	..	..	-0.9 +1.4	..	..	..	..	-0.4 +0.8	..	....	0 +0.2	-0.9 +1.4	14 yr., 5 mo.	
14	16 yr., 9 mo.	..	..	..	-2.4 0	-1.2 +0.8	-1.2 +0.8	-1.2 +0.7	-2.4 0	-1.5 -0.1	-1.3 +0.8	-0.5 +0.8	-2.4 +0.8	14 yr., 7 mo.	
15	17 yr., 2 mo.	..	..	-2.7 +1.2	..	..	..	..	-3.0 -0.3	..	-1.6 +0.8	-1.0 +1.2	-3.0 +1.2	15 yr.	
16	18 yr., 1 mo.	..	..	..	..	..	..	..	..	-2.1 +0.5	-1.5 +1.3	....	-2.1 +1.3	15 yr., 3 mo.	
17	18 yr., 7 mo.	..	..	..	..	+1.0	+2.0	..	..	+1.0	....	....	+2.0	13 yr., 8 mo.	

Errors in Prediction of Height (Uncorrected)

Average maximum error.....  
50 per cent under.....  
75 per cent under.....  
90 per cent under.....  
Range.....

2.18 in. (5.53 cm.)  
2.0 in. (5.08 cm.)  
2.8 in. (7.02 cm.)  
3.5 in. (8.89 cm.)  
5.2 in. (5.08 cm.)

Errors in Prediction of Height with Theoretic Correction of Chronologic Age of Menstruation to Thirteen and a Half Years

Average maximum error.....  
50 per cent under.....  
75 per cent under.....  
90 per cent under.....  
Range.....

1.5 in. (3.81 cm.)  
1.4 in. (3.56 cm.)  
2.0 in. (5.08 cm.)  
2.2 in. (5.59 cm.)  
2.4 in. (6.10 cm.)

\* Lower figures represent corrections.

TABLE 2.—Errors in Height Prediction of Girls for Whom the Age at Which Menstruation Began Was Not Known

Patient	Final Age	5 Yr.	6 Yr.	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	13 Yr.	14 Yr.	15 Yr.	Maximum Error	Comment
1	18 yr., 4 mo.	+2.5	+2.0	.....	+1.5	+1.5	.....	+1.3	+1.2	.....	.....	+0.1	+2.5	Congenital heart disease
2	17 yr., 5 mo.	0	.....	.....	0	+0.6	+1.2	+1.0	+1.0	.....	+0.5	+0.3	+1.2	Rheumatic heart disease
3	20 yr., 2 mo.	.....	-1.0	.....	.....	.....	.....	-0.5	.....	+0.3	.....	0	-1.0	
4	17 yr., 8 mo.	.....	.....	+0.3	.....	.....	.....	-0.8	-0.8	.....	-1.0	.....	-1.0	
5	16 yr., 8 mo.	.....	.....	-1.5	.....	-1.1	-0.8	.....	-0.6	-1.2	-0.6	-0.2	-1.5	
6	17 yr., 4 mo.	.....	.....	+0.4	+0.3	+0.3	+0.7	-0.7	-1.0	-1.2	.....	-1.0	-1.2	
7	16 yr., 11 mo.	.....	.....	.....	-0.6	+0.8	.....	+0.3	+0.8	.....	+0.4	.....	+0.8	
8	16 yr., 6 mo.	.....	.....	.....	+1.1	.....	+0.5	+0.4	+0.2	+0.9	.....	+0.5	+1.1	
9	18 yr., 5 mo.	.....	.....	.....	.....	+1.1	+1.3	+1.6	+1.5	+1.3	+1.3	+0.7	+1.6	
10	17 yr., 0 mo.	.....	.....	.....	.....	-3.0	.....	-1.2	.....	.....	-0.2	+0.2	-3.0	Menstruation began late
11	16 yr., 7 mo.	.....	.....	.....	.....	+1.7	.....	0	.....	0	+1.8	.....	+1.8	
12	17 yr., 7 mo.	.....	.....	.....	.....	.....	.....	+0.5	+1.3	+0.4	0	-0.5	+1.3	
13	16 yr., 9 mo.	.....	.....	.....	.....	.....	+1.2	.....	+2.1	+1.7	+1.4	+1.2	+2.1	
14	18 yr., 8 mo.	.....	.....	.....	.....	.....	.....	.....	-1.0	-0.4	-0.4	+0.5	-1.1	
15	19 yr., 4 mo.	.....	.....	.....	.....	.....	.....	.....	-0.2	.....	+0.2	0	+0.2	
16	19 yr.	.....	.....	.....	.....	.....	.....	.....	.....	+1.1	+0.5	+0.4	+1.1	
Totals for Tables 1 and 2 (33 Girls)														
Average maximum error.....														1.92 in. (4.88 cm.)
50 per cent under.....														1.6 in. (4.06 cm.)
75 per cent under.....														1.8 in. (4.57 cm.)
90 per cent under.....														3.0 in. (7.62 cm.)
Range.....														5.2 in. (13.31 cm.)

TABLE 3.—Errors in Height. Prediction of Boys

Patient	Final Age	5 Yr.	6 Yr.	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	13 Yr.	14 Yr.	15 Yr.	16 Yr.	Maximum Error	Comment
1	19 yr., 1 mo.	+0.5	-0.9	-0.8	+0.5	-1.4	+0.9	.....	.....	.....	.....	+2.0	.....	+2.0	
2	22 yr.	.....	-0.5	0	0	+0.5	+0.6	.....	+0.6	+0.1	.....	+1.0	.....	+1.0	(?) Hypopituitary; bone age, 17 yr. at 15 yr., 4 mo.
3	18 yr., 7 mo.	.....	-1.0	-1.0	.....	.....	.....	.....	+1.5	.....	+3.6	+2.5	+1.0	+3.6	Italian
4	18 yr., 3 mo.	.....	-0.5	+0.3	+0.5	+0.6	.....	.....	.....	.....	+2.5	+1.8	+1.5	+2.5	Italian
5	20 yr., 10 mo.	.....	.....	.....	.....	.....	+2.8	+2.8	+3.0	+2.8	+2.8	.....	.....	+3.0	(?) Hypopituitary; bone age, 11 yr. at 10.5 yr.
6	17 yr., 7 mo.	.....	.....	.....	.....	-1.0	.....	.....	-0.8	+0.2	+0.5	+1.2	+1.2	+1.2	
7	17 yr., 6 mo.	.....	.....	+0.6	0	0	+1.0	.....	-0.3	.....	+0.6	+0.4	.....	+1.0	
8	17 yr., 9 mo.	.....	.....	.....	.....	0	0	+1.4	+1.4	+0.6	0	0	+0.6	+1.4	
9	17 yr., 10 mo.	.....	.....	.....	.....	.....	.....	.....	0	-1.2	-1.2	-1.2	.....	-1.2	
10	17 yr., 7 mo.	.....	.....	.....	.....	-1.0	-0.2	+0.5	-0.5	-1.0	-1.4	-0.8	-1.8	-1.4	
11	17 yr., 8 mo.	.....	.....	-2.4	.....	.....	.....	.....	.....	+1.4	.....	+2.0	+0.8	-2.4	
12	18 yr., 10 mo.	.....	.....	.....	.....	.....	.....	.....	.....	.....	-1.8	-1.8	.....	-1.8	Bone age, 14 yr., 3 mo. at 15.8 yr.; corrected to -0.8
Average maximum error.....															1.87 in. (4.75 cm.)
50 per cent.....															1.4 in. (3.56 cm.)
75 per cent.....															2.5 in. (6.35 cm.)
90 per cent.....															3.6 in. (9.14 cm.)
Largest error .....															3.6 in. (9.14 cm.)



In light of these observations, we reexamined our data and found that the greatest errors in the prediction of height were made in the cases of girls who began menstruation at ages other than  $13\frac{1}{2}$  years. It was noted that in the cases of those who began menstruation earlier than  $13\frac{1}{2}$  years, the predictions were always greater than the height actually attained. The reverse was true for those who began menstruation after the age of  $13\frac{1}{2}$  years. In 17 of the 33 girls, the age at which menstruation began was known. In these cases, the difference between the age of  $13\frac{1}{2}$  years and the age at which menstruation began was added to the chronologic age if menstruation was early and subtracted if it was late. Other errors were determined in a similar manner by adjusting and plotting the various ages on the graphs (table 1). This changed the percentile standings so that the errors in height prediction were markedly decreased, especially within two to three years of the time of menstruation. In this series, it was noted also that each child tended to maintain either a positive or a negative error throughout the period of growth. This indicates that a child usually remains advanced or retarded in sexual maturation during the entire period of growth. In our group of children, a few bone age studies had been made during the growth period; this decreased the errors in the prediction of final height. In the boys, bone maturation ages were available in 3 cases, and these gave a similar correction of the error in prediction of height at the time the bone age had been taken.

A fairly accurate prognostication of final height can be made in the individual child by using the percentile chart. It can be made more accurate by determination of the degree of skeletal maturation and by substituting the bone maturation age for the chronologic age. According to Todd's standards, the bone age can be determined with a deviation of not more than six months. Therefore, if the bone age is more than six months advanced or retarded from the chronologic age, the bone age should be substituted for the chronologic age.

An accurate estimate of the probable final stature of any child is of value to the orthopedic surgeon in planning operative treatment in cases of inequality of leg length. For instance, shortening of the leg or epiphysial arrest might be unwise in a child who promises to be extremely short at the completion of growth. On the other hand, in a child who is likely to be extremely tall, shortening procedures would be preferable to lengthening ones because of the comparative simplicity of the shortening procedure.

#### PREDICTION OF THE ADULT PROPORTIONS OF THE FEMUR AND THE TIBIA TO STATURE IN THE INDIVIDUAL PATIENT

From available data, we can arrive at significant and useful conclusions regarding the prediction of the final proportions of the femur

TABLE 4.—Errors in Height Prediction of Girls (Not Followed to Complete Growth) with Theoretic Correction of Chronologic Age of Menstruation of Thirteen and a Half Years

Patient	Final Age	5 Yr.	6 Yr.*	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	13 Yr.	14 Yr.	15 Yr.	Maxi- mum Error	Age at Which Menstruation Began	Comment		
1	15 yr., 3 mo.	.....	.....	-0.9 -0.6	-0.9 -0.5	+0.9 -0.5	+1.0 -0.3	+2.0 +0.6	+2.5 +0.8	+1.5 +0.5	+1.5 +0.6	+1.2 +0.7	+2.5 +0.8	12 yr., 4 mo.			
2	16 yr.	.....	.....	.....	+1.5 +0.6	.....	+2.0 +1.5	.....	+2.9 +1.8	+2.2 +1.5	+1.5 +0.8	+0.7 +0.4	+2.9 +1.8	13 yr.			
3	15 yr., 10 mo.	.....	.....	.....	.....	+3.0 +1.8	+3.0 +1.6	+3.0 +1.6	+3.0 +1.8	+3.0 +2.0	+1.8 +1.0	+1.5 +2.0	+3.0 +2.0	12 yr., 5 mo.			
4	15 yr., 9 mo.	.....	.....	.....	.....	.....	.....	+2.2 +1.6	+2.4 +1.6	+2.6 +1.8	+1.8 +1.5	+0.9 +0.5	+2.6 +1.8	13 yr., 1 mo.	Spanish		
5	16 yr.	.....	.....	.....	.....	.....	.....	.....	+1.8 +0.8	+0.8 +0.4	+1.2 +0.8	+0.9 +0.6	+1.8 +0.8	13 yr.			
6	11 yr., 1 mo.	.....	.....	.....	.....	.....	.....	+2.6 -1.0	+2.7 -0.4	+2.3 +0.8	+1.8 +0.4	.....	+2.7 -1.0	11.6 yr.			
7	15 yr., 5 mo.	.....	+1.5 -1.5	+2.1 -0.7	+2.3 -0.5	+2.7 -0.3	.....	+4.2 +0.5	+3.1 +0.5	+2.4 +0.4	+2.0 +0.4	+1.0 +0.1	+4.2 -1.5	11.9 yr.			
8	15 yr., 3 mo.	.....	-0.4	.....	+1.1	+0.7	.....	+0.5	-0.3	-0.3	+0.3	+1.0	+1.1	?			
9	14 yr., 10 mo.	.....	.....	.....	.....	+2.0	+2.5	+2.5	+2.5	+2.4	+2.0	.....	+2.5	?	Rheumatoid arthritis		
10	14 yr., 8 mo.	.....	.....	.....	.....	+2.5	+2.8	+2.8	.....	.....	.....	+1.5	+2.8	?			
11	15 yr., 11 mo.	.....	.....	.....	.....	.....	+3.0	+3.0	+3.2	+2.8	+1.4	+1.0	+3.2	?	Chinese; tuberculosis		
12	15 yr., 3 mo.	.....	.....	.....	.....	.....	.....	-1.1	-0.7	+0.7	+1.2	+0.8	+1.2	13 yr., 5 mo.	Rheumatic fever		
Errors in Height Prediction in the 8 Cases in Which the Age of the Beginning of Menstruation is Known															Errors in Height Prediction Corrected by Considering the Age at Which Menstruation Began as 13.5 Years		
															Average maximum error.....		1.36 in. (3.45 cm.)
															50 per cent under.....		1.2 in. (3.05 cm.)
															90 per cent under.....		1.8 in. (4.57 cm.)
															Largest error .....		2.0 in. (5.08 cm.)

\* Lower figures represent corrections.

and the tibia to the total stature of individual patients even though a complete teleroentgenographic study of the growth of these two bones has never been made in individual children.

Meredith<sup>9</sup> and Boynton<sup>24</sup> showed that the average variation of the proportions of total leg length to stature is small from the ages of 7 to 17 years (fig. 6). Schwerz<sup>14</sup> likewise found that the average variation of the proportions of the femur and the tibia to stature was small from the ages of 6 to 14 years, the limits of his material (fig. 4).

Schultz<sup>13</sup> noted, in comparing Negro and white fetuses, that the proportion of the length of the legs to the body was larger in the Negro. The same is true of Negro adults as compared with white adults. If racial trends in bodily proportions are laid down in infancy, this should be true also of individual bodily proportions. Maresh and Deming<sup>25</sup> took teleroentgenographic measurements of infants from birth to the

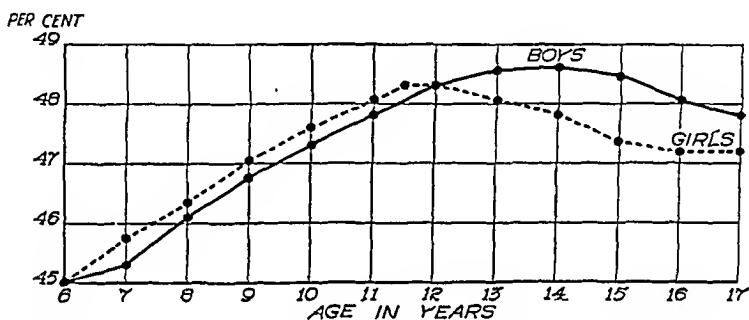


Fig. 6.—Leg length as percentage of stature as drawn from data of Meredith.

age of 6 months. They found that the curves of growth for the bones of different children were parallel during the entire period and that in each child the relation in length between any two bones of the body remained constant in a remarkable number of cases.

Baldwin studied the relation between the sitting height and the standing height of individual patients between the ages of 10 and 15 years. He found that this relation was remarkably constant and that the children maintained their group rating in this proportion more closely than in any other bodily characteristic. If this is true for the relation

24. Boynton, B.: *The Physical Growth of Girls: A Study of the Rhythm of Physical Growth from Anthropometric Measurements on Girls Between Birth and Eighteen Years*, Studies in Child Welfare, Iowa City, University of Iowa, 1936, vol. 12, no. 4.

25. Maresh, N. M., and Deming, J.: *The Growth of the Long Bones in Eighty Infants: Roentgenograms Versus Anthropometry*, Child Development 10:91 (June) 1939.

between the sitting height and the standing height, it must be true for the length of the legs, since this measurement was derived by subtraction of the sitting height from the total stature. Wallis confirmed this in a study of 54 boys and 49 girls who were followed individually for five years between the ages of 3 and 12 years.<sup>12</sup> She concluded that the person's constitutional type tends to persist in spite of variation in age through at least seven years of preadolescent growth, the limits of her material. In addition, she noted that the children maintained their own bodily pattern more closely than that of their parents.

In view of these data, it may be concluded that a child maintains the relative proportions of the femur and the tibia to stature with only small age variations. For this reason, the surgeon can estimate the probable adult proportions of these bones to stature by taking a child's present proportions and adding small age changes.

The subtable in figure 5 is a table of additions to the present percentage of the femur and the tibia to the stature. These figures are to be added to the calculated present percentages of these bones to stature according to the age and the sex in order to determine the probable adult percentage of the length of the femur and the tibia to the stature in a child. This table was compiled from the incomplete data of Meredith, Boynton, Schwerz and Davenport and will be modified as more accurate information on the growth of children is accumulated. For our purpose, these changes by age are so small that the final length of the femur and the tibia could be determined fairly accurately in the later postnatal period of growth by multiplying the present proportions of these bones to the stature by the predicted height. However, because these age changes, though small, are definite, they should be considered in order to increase the accuracy of our calculations. By the use of this table, the final proportions of the femur and the tibia to the stature will probably be predicted with an error of less than 0.5 per cent in the prediction of the final length of either the femur or tibia.

#### PERCENTAGE OF GROWTH FROM THE PROXIMAL AND THE DISTAL EPIPHYSIAL CARTILAGES

At the present time, the only work available to determine the actual percentage of growth from the ends of the long bones is that of Digby, Bisgard and Bisgard<sup>26</sup> and Payton.<sup>27</sup> Digby's method (fig. 7 A) was used in an unstated number of dried human bones. The Bisgards implanted metal shots in living goats, and the figures obtained were

26. Bisgard, J. D., and Bisgard, M. E.: Longitudinal Growth of Long Bones, *Arch. Surg.* **31**:569 (Oct.) 1935.

27. Payton, C. G.: The Growth in Length of the Long Bones in the Madder-Fed Pig, *J. Anat.* **66**:414 (April) 1932.

checked against Digby's method in dried bones (fig. 7 *B*). Payton fed madder to growing pigs. The relative similarity of the figures obtained by these methods in human beings, goats and pigs is interesting

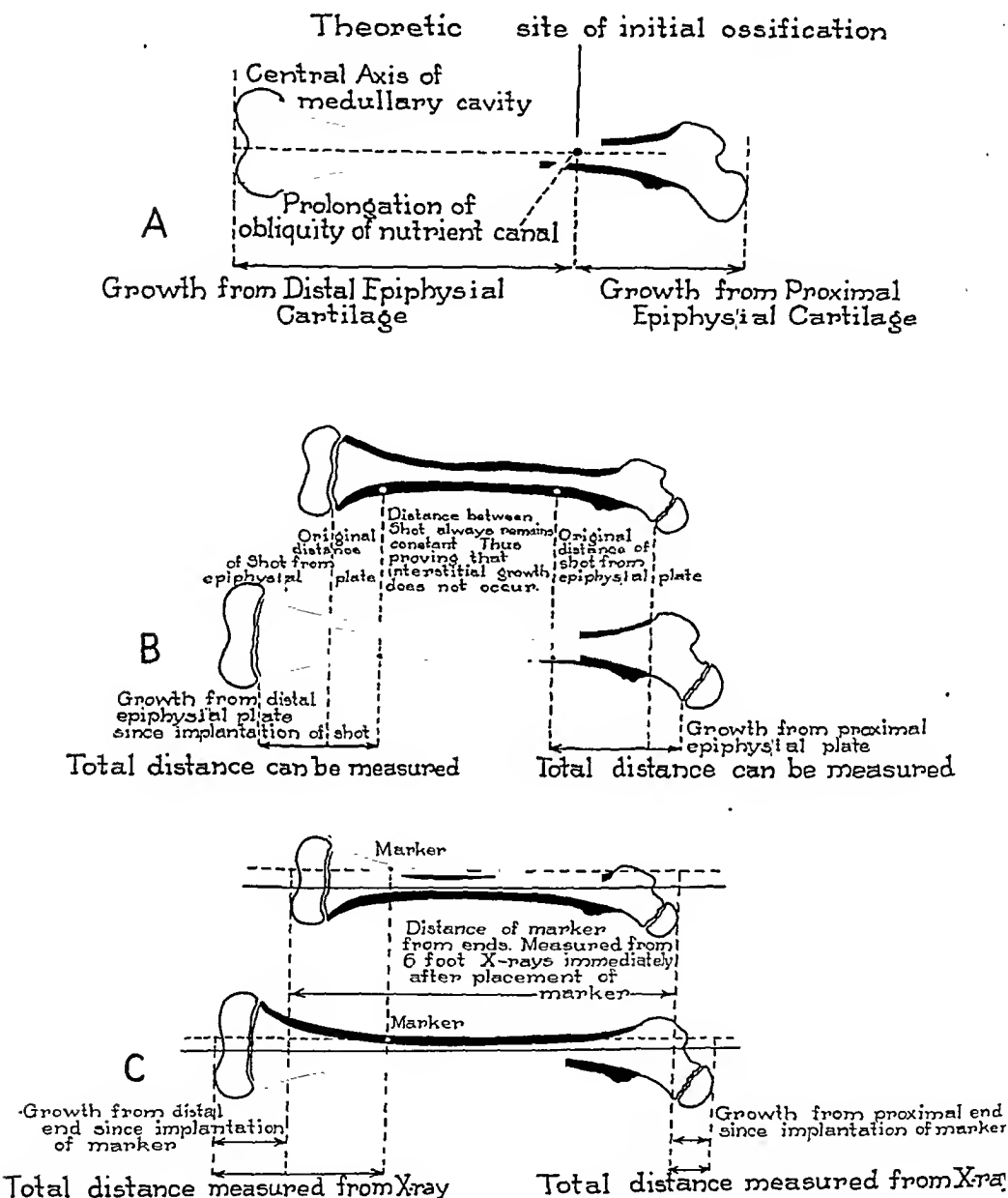


Fig. 7.—Diagram illustrating various methods of determining the percentage of growth from each end of the long bones. *A*, Digby's nutrient canal method of calculating percentage of growth from each end of a long bone. *B*, Bisgards' shot method of determining percentage of growth from each epiphysial cartilage. *C*, method of determining the percentage of growth from each end of the bones in growing children.

(table 5). Although Digby's method is open to considerable criticism,<sup>28</sup> it is probably fairly accurate for human beings.

In goats and pigs, it is noted that in prenatal and early postnatal life the percentages contributed from each end of a bone are more nearly equal than in later life. However, from the work of the Bisgards it appears that the relative percentages of growth from each end of the bone are constant during the postnatal period. In human beings, there is some indication that the proportion of growth from each end of the bone is somewhat more equal in prenatal life and early postnatal life than in later postnatal life. In 1 instance, bismuth had been prescribed for a pregnant woman during the last five months of pregnancy. This resulted in transverse lines being laid down across the long bones of the infant. These lines showed that the proportion of growth for the

TABLE 5.—*Comparison of Percentage Growth from Various Epiphyses as Determined by Various Authors*

Author	Subject	Method	Femur		Tibia		Humerus		Radius		Ulna	
			Proximal	Distal	Proximal	Distal	Proximal	Distal	Proximal	Distal	Proximal	Distal
Digby <sup>7</sup> .....	Human	Nutrient canal	31.2	68.9	57.1	42.9	80.8	19.2	25	75	18.6	81.4
Bisgard and Bisgard <sup>26</sup>	Goats	Shots to epiphysal plate	35.8	64.2	54.8	45.2	82	18	25.5	74.5	18.8	81.2
	Goats	Nutrient canal	32.7	67.3	56	44	81.7	18.3	25.5	74.5	19.6	80.4
Payton <sup>28</sup> ...	Pigs	Madder fed	37.2	62.8	71.8	28.2	78.8	21.2	20.8	79.2	31	69

last five months of prenatal life in the upper and lower ends of the femur was 46:54 and 50:50 for the upper and lower ends of the tibia. In the first five months of postnatal life, the proportion of growth was 40.6:59.3 for the femur and 38:62 for the tibia. From lines of arrested growth, Harris determined that the proportion of growth in the tibia of a child between the ages of 3½ and 5½ years was 51.4:48.6. The greatest amount occurred at the upper end.<sup>29</sup> By the use of vitallium markers, which will be described in a later paragraph, in the case of a Negro boy, we determined that the percentage for the femur was 37:63 and for the tibia 53:47 between the ages of 5 and 5½ years (fig. 7 C and 14). From lines of arrested growth in a Chinese girl, we found that the percentage for the tibia was 55:45 between the ages of 4 and

28. Payton, C. G.: The Position of the Nutrient Foramen and Direction of the Nutrient Canal in the Long Bones of the Madder Fed Pig, *J. Anat.* 68:500 (July) 1934.

29. Harris, H. A.: The Growth of the Long Bones in Childhood, *Arch. Int. Med.* 38:785 (Dec.) 1926.

6½ years. In another patient, two lines of arrested growth resulting from two successive injuries at known times were found in the metaphysis of the normal femur. In this case we were able to determine that the percentage of growth from the distal end of the femur was 70 per cent between the ages of 8 and 10 years (fig. 8). This figure is close to Digby's figures. At the present time our experience convinces us that the following percentages of growth may be accepted until more exact studies have been made on human beings by the implantation of metal markers in the long bones (fig. 7 C and 14):

Femur: proximal end, 30 per cent; distal end, 70 per cent

Tibia: proximal end, 55 per cent; distal end, 45 per cent

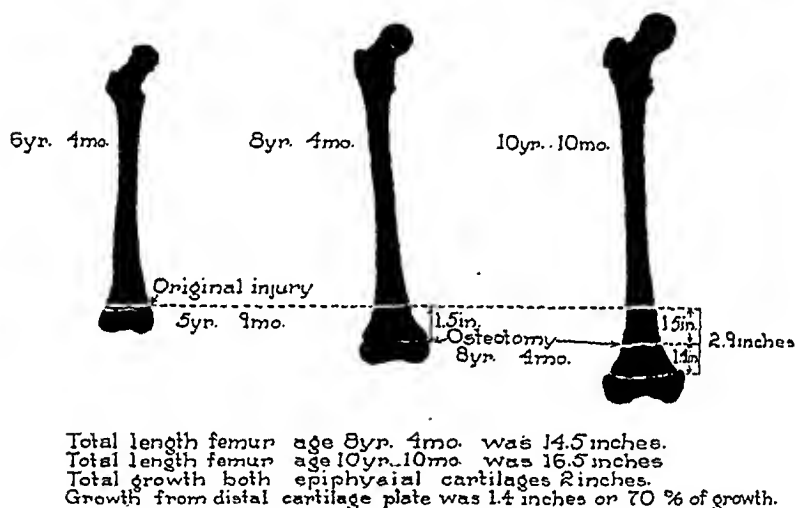


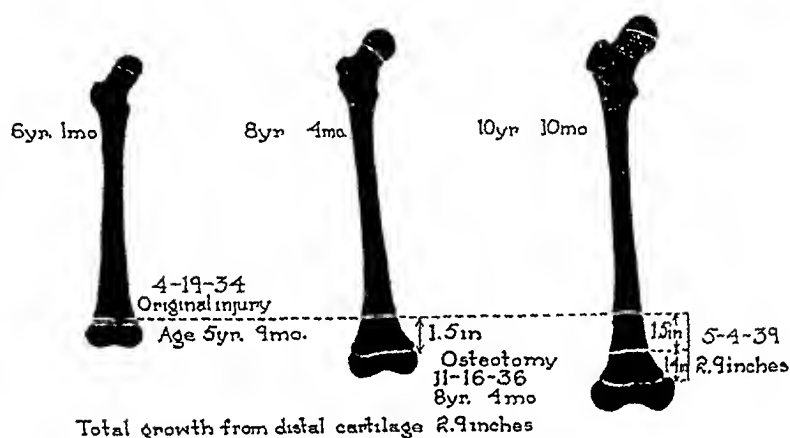
Fig. 8.—Estimation of the percentage of growth from the epiphysial cartilages of a normal femur; calculation is made from lines of arrested growth appearing after two specific injuries.

As mentioned before, we believe that growth should be estimated separately from the respective ends of each bone because of the changes in the relative rates of growth of the femur and the tibia. Since this method of estimating the normal growth of the bones has been developed only recently, we have not had an opportunity for follow-up work in a sufficient number of cases to check its accuracy in the individual child.

The following case reports and accompanying diagrams illustrate cases in which the growth or the loss of growth from individual epiphyses of the long bones has been measured. In these cases, we were able to compare the actual loss of length with the amount estimated to occur from these centers by reversing our method. In other words, we have calculated the expected length of the bones at an earlier age from the patient's measurements at the present time.

## REPORT OF CASES

CASE 1.—R. J. (fig. 9), a boy 10 years and 10 months of age, suffered a severe injury at the age of 5 years and 9 months; at that time a line of arrested growth was laid down in the femur. At 8 years and 4 months, a major operation caused another line of arrested growth to appear in the same bone. Measurements based on the lines of arrested growth showed that the growth from the distal femur had been: 1.5 inches (3.81 cm.) from the age of 5 years and 9 months to the age of 8 years and 4 months and 1.4 inches (3.57 cm.) from the age of 8 years and 4 months to the age of 10 years and 10 months.



## COMPARISON WITH OUR METHOD

Data  
 Stature—(10yr 10mo) 59.5 inches  
 Normal Femur 16.5 inches or 27.9% stature  
 Estimation  
 Stature—(5yr 9mo) 47.7 inches  
 Femoral% (decreases 0.5) = 27.4%  
 Calculation  
 Femoral Length—(5yr 9mo) =  $47.7 \times 27.4\% = 13$  inches  
 Growth entire femur =  $16.5 - 13 = 3.5$  inches  
 Growth distal femur =  $3.5 \times 0.7 = 2.5$

Fig. 9.—Diagram made from roentgenograms showing the amount of longitudinal growth contributed by the distal femoral epiphysis as shown by lines of arrested growth appearing after specific injuries.

Other available measurements were:

Age	Height	Length of Femur	Femoral Percentage of Stature
5 yr., 9 mo.	46.5 in. (118.11 cm.)	Not known	....
8 yr., 4 mo.	52.75 in. (133.99 cm.)	14.5 in. (36.83 cm.)	27.5
10 yr., 10 mo.	59.5 in. (151.13 cm.)	16.5 in. (41.91 cm.)	27.9

If we had seen the patient at the age of 8 years and 4 months, the growth at the age of 10 years and 10 months could have been calculated in the following manner:

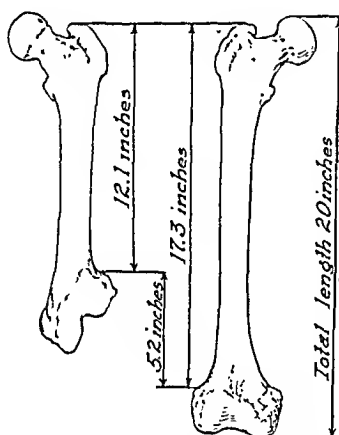
The femoral percentage at 8 years and 4 months was 27.5. The height at 10 years and 10 months was estimated to be 58.6 inches (148.82 cm.), and the femoral percentage was expected to increase to 28 per cent. Therefore, the calculated femoral length at 10 years and 10 months would have been 28 per cent  $\times$  58.6 or



16.4 inches (41.67 cm.). This compared closely with the actual length that the femur attained. The growth from the distal part of the femur would have been  $1.9 \times 0.7$  or 1.3 inches (3.3 cm.). This is close to the actual growth of 1.4 inches (3.55 cm.) from the distal part of the femur.

It is possible to calculate backward from the age of 10 years and 10 months to the age of 5 years and 9 months in order to compare the expected growth with the amount which actually occurred. This is shown in figure 9. The calculated growth was 2.5 inches (6.35 cm.) as compared with the actual growth of 2.9 inches (7.37 cm.), an error of 0.4 inches (1.02 cm.) for a period of five years of growth.

CASE 2.—C. V. (fig. 10), a man 24 years of age, at the age of 6 years had suffered a fracture involving the lateral portion of the distal epiphysis of the femur. Owing to the premature fusion of the lateral portion of this epiphysis, severe valgus deformity of the knee developed. Teleroentgenograms were taken of both femurs. Comparative measurements revealed a loss of 5.2 inches (13.21 cm.) in growth from the distal femoral epiphysis between the age of 6 years and full



#### Comparison with our Method

##### Data.

Stature—(Adult) 69.5 inches.

Normal femur 20 inches or 28.8% Stature.

##### Estimation.

Stature—Age 6 y. 45.25 inches

Tibial % decreases 2% = 26.8%

##### Calculation—

Femoral length (Age 6 y.) =  $45.25 \times 26.8\% = 12.1$  in.

Growth entire femur =  $20 - 12.1 = 7.9$  inches.

Growth distal femur =  $7.9 \times 0.7 = 5.5$  inches.

Fig. 10.—Diagrams from teleroentgenograms demonstrating deformity and loss of length after premature closure of the lateral portion of the distal femoral epiphysis from age of 6 to full growth.

growth. Available measurements of this patient's height in early life were as follows:

3 yr., 6 mo.—42 in. (106.68 cm.), estimated from final height and percentile chart for stature to have been 39.5 in. (100.33 cm.);

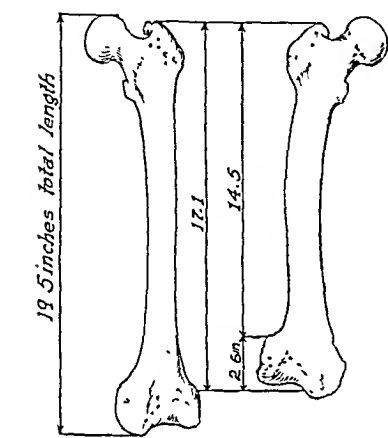
4 yr., 6 mo.—43 in. (109.22 cm.), estimated from final height and percentile chart for stature to have been 42 in. (106.68 cm.);

10 yr., 6 mo.—55.5 in. (140.97 cm.), estimated from final height and percentile chart for stature to have been 54.6 in. (138.68 cm.).

From the patient's height and the length of the normal femur at the present time, the theoretic growth from the distal epiphysis of the femur (fig. 10) would have been 5.5 inches (13.97 cm.), an error of 0.3 inches (.762 cm.) over a period of eleven or twelve years of growth.

CASE 3.—L. H. (fig. 11), a young man 17 years and 8 months of age, at the age of 12 years had sustained a fracture involving the lateral portion of the distal epiphysis of the right femur. Valgus deformity occurred as a result of premature fusion of the lateral portion of the epiphysal plate.

In September 1936, a cuneiform osteotomy of the femur was performed; the base of this included the medial side of the distal epiphysial cartilage. This resulted in fusion of the entire epiphysial cartilage plate. This osteotomy gave fair correction of the deformity but did not change the length of the femur on the lateral side.



#### Comparison with our Method

##### Data

Stature—(Age 17yr. 8mo.) 68 inches  
Normal Femur—19.5 inches or 28.7 % stature

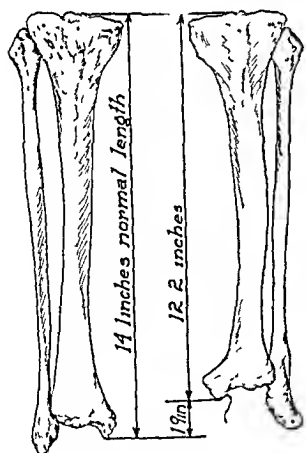
##### Estimation

Stature—(Age 12) 56.5 inches  
Femoral % (decreases 1%) = 27.7 %

##### Calculation

Femoral Length—(Age 12) =  $56.5 \times 27.7\% = 15.7$  inches.  
Growth entire Femur— $19.5 - 15.7 = 3.8$  inches  
Growth distal Femur— $3.8 \times 0.7 = 2.66$  inches

Fig. 11.—Diagrams from teleroentgenograms demonstrating deformity and loss of length after premature closure of the lateral portion of the distal femoral epiphysis from the age of 12 to the age of 17 years and 8 months. When the patient was 14 years of age, closing osteotomy was performed on the medial side; this effected a decrease in the deformity but did not bring about a decrease in length on the lateral side.



#### Comparison with our Method

##### Data

Stature—(16yr. 4mo.) 64.25 inches.  
Right Tibia—14.1 inches or 22 % Stature.

##### Estimation.

Stature (11yr. 10mo.) 53.6 inches.  
Tibial % (increases 0.5%) = 22.5 %

##### Calculation.

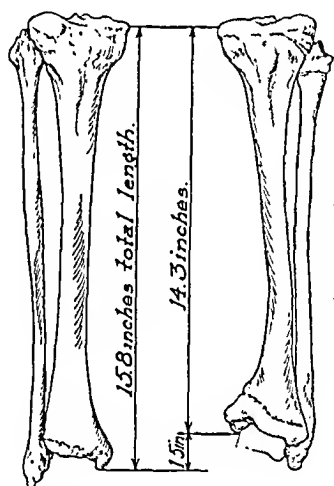
Tibial length (11yr. 10mo.) =  $53.6 \times 22.5\% = 12.1$  in

Fig. 12.—Diagrams from teleroentgenograms demonstrating actual loss of length after closure of both epiphyses of the tibia from the age of 11 years and 10 months to the age of 16 years and 4 months.

Comparative measurements taken from the greater trochanter to the lateral epicondyle of each femur showed a loss of 2.6 inches (6.6 cm.) in length. From the length of the normal femur and the patient's height at the present time, the estimated growth from the distal epiphysial cartilage of the femur was 2.66 inches (6.76 cm.).

CASE 4.—E. M., (fig. 12), a youth 16 years and 4 months of age, at the age of 11 years and 10 months suffered severe burns of his left leg which became infected. Osteomyelitis occurred and destroyed the distal epiphysis of the tibia. At the time of writing, the length of the medial side of the left tibia is 12.2 inches (31 cm.), which probably approximates the length at the time of the burn. By our method, the length of the tibia at the age of 11 years and 10 months was calculated to be 12.1 inches (30.73 cm.).

CASE 5.—C. P. (fig. 13), a youth 16 years and 9 months of age, at the age of 10 years sustained a fracture which destroyed the medial portion of the distal epiphysis of the tibia. Measurements revealed a loss of 1.5 inches (3.81 cm.) of growth from the medial side of the tibia. From the length of the normal tibia and his present height, it was calculated that the growth which took place from the normal epiphysial cartilage plate of the lower tibia between the ages of 10 years and 16 years and 9 months was 1.35 inches (3.43 cm.).



#### Comparison with our Method

##### Data.

Stature—(15yr 9mo.) 69.5 inches

Normal Tibia 15.8 inches or 22.8% stature.

##### Estimation

Stature—(age 10) 56.3 inches

Tibial %—(no change)—22.8 %

##### Calculation

Tibial length (age 10) =  $56.3 \times 22.8\% = 12.8$  inches

Growth entire Tibia =  $15.8 - 12.8 = 3$  inches.

Growth distal Tibia =  $3 \times 0.45 = 1.35$  inches.

Fig. 13.—Diagrams from teleroentgenograms demonstrating deformity and loss of length after premature closure of the medial portion of the distal tibial epiphysis from the age of 10 years to the age of 15 years and 9 months.

#### ESTIMATE OF THE EXPECTED GROWTH OF THE ABNORMAL LIMB

It should be emphasized that any final inequality in the length of the legs is dependent on the growth of the abnormal limb with relation to the growth of the normal one. By the method outlined, the expected growth of the normal limb can be determined with a reasonable degree of accuracy. This is a valuable aid in estimating the growth of the shorter leg. In every case, a careful study should be made of the mechanism which produces the inequality and its relation to the growth of the individual epiphyses. There are three such mechanisms: (1) disturbances confined to specific epiphysial plates; (2) disturbances affecting the rate of growth of all of the epiphyses of the limb; (3) mechanical loss in length.

*Disturbances Confined to Specific Epiphysial Plates.*—(a) Complete Premature Closure of One or More Epiphyses: Complete premature closure of one or more epiphyses is usually a result of trauma, such as a fracture crossing the epiphysial cartilage or a crushing injury of this structure. It may also be caused by roentgen therapy or operative procedures in the vicinity or at the site of the epiphysis. Destruction of the epiphysial cartilage by tuberculosis or osteomyelitis is frequent, but involvement of the epiphyses by tumors is less common.

Complete premature closure of an epiphysis during the period of growth results in the loss of the longitudinal growth which that epiphysis would have contributed. Calculation as to the loss of growth is a simple matter because the undamaged centers are usually growing at a normal rate. Therefore, the final length will be the normal growth minus the expected growth from the closed epiphysis which may be calculated entirely on the normal expectancy of growth in that bone.

Operative closure of the corresponding epiphysial plate on the sound bone will immediately fix the inequality and prevent it from increasing. This inequality may be decreased by the fusion of other epiphysial plates of the normal leg. The calculations are made on the basis of the growth of the normal leg except possibly in those cases caused by infection. In children 6 to 8 years of age, an injury involving the lower epiphysis of the femur may cause a loss in growth of 4 to 6 inches (10.16 to 15.24 cm.). At such an early age, it is probably unwise to fuse the corresponding epiphysis of the normal limb, especially if the child is likely to become a short adult. In these cases, leg lengthening may be indicated.

(b) Incomplete Closure of One Epiphysial Cartilage Plate: Incomplete or partial closure of an epiphysis is generally due to injury. Angular deformities develop with the growth of the undisturbed portion of the epiphysis. Epiphysial arrest of the entire plate will prevent an increase in deformity. In certain instances, however, in which the loss resulting from this procedure would be too great, a series of osteotomies may be planned in order to gain length from this unilateral growth.

(c) Alteration in the Rate of Growth of One Epiphysis: Increase in the rate of growth of a single epiphysis may be caused by damage from operative intervention or a decrease in its blood supply from the same cause. Alteration in the rate of growth may occur also when there is juxtaepiphysial osteomyelitis. An increase in the rate of growth of an epiphysial plate may be due to increased vascularity from localized osteomyelitis or a tumor of the hemangiomatous type in the metaphysial region. If the lower epiphysis of the femur had been so affected in early childhood, severe inequality might result. To determine the relative rates of growth of the two sides, metal markers may be placed in the shafts of both femurs and tibias for the purpose of recording measure-

ments. If the inequality in length already present is equal to the expected growth of the corresponding epiphysial plate, then this epiphysis may be fused and the inequality kept from increasing.

*Disturbances Affecting the Rate of Growth of All the Epiphysial Plates of the Limb.*—(a) Epiphysial Plates Intact with Growth at a Decreased Rate in Comparison with the Normal Limb: This is the most common mechanism producing inequality in the length of legs. A number of factors may play a part, the most important of which is defective circulation with lowered local temperature and disuse. This mechanism frequently follows poliomyelitis but may be caused also by any long-standing disabling condition in the extremity. Great difficulty is often encountered in these cases in estimating the comparative rates of growth of the normal and abnormal limbs. In a general way, it is known that the loss of growth of the limb is related to a decrease of local temperature which, in turn, is probably caused by vasomotor changes. Furthermore, the shortening is usually greater in cases with the greatest degree of muscular paralysis. The tibia ordinarily shows the largest loss of growth since the most marked vasomotor changes and residual paralysis are generally found in the distal portion of the extremity. Despite these general impressions, it is not yet determined whether the rate of growth is affected as a whole or whether there is a disturbance in the normal ratios of growth between the proximal and distal ends of the long bones. As a rule, such calculations can be made only in rare instances in which lines of arrested growth appear in the long bones. Unfortunately, accurate calculations cannot often be made from these lines because they are seldom of sufficient density and the time of their appearance is frequently indefinite. For this reason, we have devised a simple method by which small markers are inserted subcutaneously into the cortex of the shafts of the femurs and the tibias. These markers can be put through the soft parts and implanted in the bones without incision. The marker is the end of a vitallium stylet which is introduced through a hypodermic needle. The stylet has a notch about  $\frac{5}{16}$  inch (0.8 cm.) from its point. It is placed within the needle with its notch projecting just beyond the end of the needle. The needle and the stylet are fixed in a drill chuck, turned through the soft parts and drilled into the bone. The depth is limited by the cuff formed by the end of the hypodermic needle. The chuck is then removed, and with the needle in place, the stylet is bent until it breaks at its notch, leaving only the point in the bone. The markers remain permanently for the measurement of comparative rates of growth of the individual epiphyses. After the introduction of the markers, teleroentgenograms are taken. Subsequent teleroentgenograms at regular intervals are compared with the original films and give the exact amounts of growth from each end

of the bones, thus permitting definite calculations of comparative rates of growth from the epiphyses (figs. 7 *C* and 14). In this way, epiphysial arrest may be carried out in a more accurate manner. Increasing study by this means will add much information to the store of knowledge regarding both normal and abnormal growth.

Some children are seen so near the completion of the period of growth that no time is allowed for such studies. If the expected growth

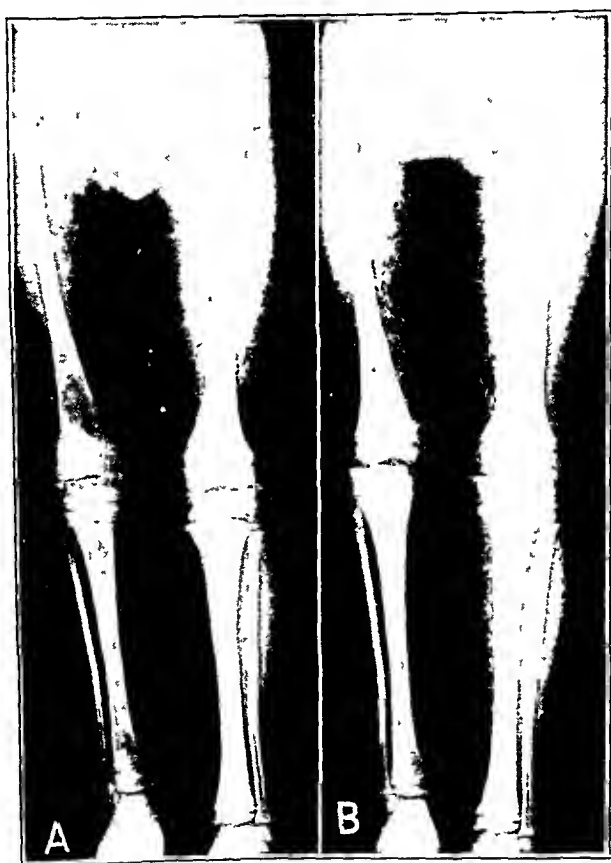


Fig. 14.—Teleroentgenograms of a Negro boy who had poliomyelitis at the age of 1 year with residual paralysis of the right leg. Vitallium markers were implanted in both femurs and tibias for the determination of the relative rates of growth of the individual epiphyses of the two legs. *A*, at 5 years of age, immediately after the implantation of the markers. *B*, at 5½ years of age.

from one or more epiphyses of the normal limb is less than or equal to the discrepancy in length already present, the epiphyses contributing this amount may be fused. The result of this procedure will depend on the rate of growth of the epiphyses of the short leg.

In many cases in which this mechanism has been present since an early age, i. e., in children from 10 to 12 years of age who had polio-

myelitis from infancy and in whom there is only 2 to 3 inches (5 to 7.6 cm.) of shortening, a period of observation is unnecessary. Simple analysis of the difference in the length of the bones in comparison with the probable growth since the onset of the disease, shows that the actual growth rate of the abnormal limb is so close to that of the normal limb that for all practical purposes the expected growth of the shorter leg may be calculated on the basis of the growth of the normal leg. From such considerations, a proper time for epiphysial arrest may be determined. If it is obvious that equalization cannot be obtained by epiphysial arrest alone, other procedures such as leg lengthening or leg shortening may be planned.

In children of short stature with healed joint disease, especially disease of the hip which has resulted in fusion of the joint, the shorter limb may be lengthened. Both the operation itself and the postoperative lengthening in such cases are relatively simple, and the functional results are good because the extremity is stable and the muscular power is usually normal.

(b) *Epiphysial Plates Intact with Growth at an Increased Rate as Compared to the Normal Limb:* This mechanism of altered growth may be caused by congenital hemangioma or post-traumatic arterio-venous aneurysm. It may also follow low grade infections of a chronic nature, such as osteomyelitis, syphilitic lesions of the bone or prolonged soft tissue infection. The factors which produce an augmented rate of growth are undoubtedly increased vascularity and increased local temperature of the limb.

*Mechanical Inequality.*—In the third group are placed those cases in which there is a loss in the length of the bone because of overriding or angulation in healed fractures, destruction of bony substance by infection or tumor or by a dislocation of the hip. To equalize the length of the legs in these cases, either reduction of the dislocation of the hip or correction of the angular deformity by osteotomy is generally indicated. If a considerable shortening still remains, other measures may be planned for the equalization of leg length. If all the epiphysial cartilages of the shorter leg are growing at a normal rate, closure of the epiphyses of the sound limb should give final equality in the length of the legs. In most of these cases, however, there is often a decrease in the rate of growth of the epiphysial cartilage or a loss of growth from its destruction. This may be determined from roentgenograms and by careful measurement from teleroentgenograms. If the determination of the rates of growth cannot be made from the teleroentgenograms alone, markers may be used. If, however, the discrepancy is great and the patient is of such age that further growth is limited, epiphysial arrest may be safely performed on the basis of the normal rates of growth.

## SUMMARY

A practical method is here presented for estimating the final height and the proportionate lengths of the femur and the tibia in individual children. This method can be effectively employed in planning operative procedures which aim to equalize the length of the extremities. By use of the skeletal maturation age, errors are eliminated which might occur if the chronologic age alone is employed.

When comparative rates of growth of the extremities are indeterminate by this method, we have found the metal markers previously described and placed in the bone by a special technic to be of great value.

Parnassus and Third Avenues.



## EARLY CARCINOMA IN THE HYPERPLASTIC THYROID

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AND

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Carcinoma of the thyroid has been the subject of numerous excellent contributions in which its various aspects and phases have been fully discussed. Information regarding the pathologic nature, the diagnosis and the treatment of this type of tumor has been greatly increased. Nevertheless, there remain many problems to be solved and large and small gaps in the knowledge of it to be filled.

A case recently observed at this hospital has drawn our attention to the well known, but curious and unexplained, fact that carcinoma of the thyroid is exceedingly rare with diffuse hyperplasia of this gland.

Coller<sup>1</sup> found a gland hyperplastic only once among 90 cases of thyroid carcinoma. Pemberton<sup>2</sup> observed diffuse hyperplasia in 10 instances of 774 cases of thyroid cancer, and Friedell,<sup>3</sup> in 12 among 412 cases. Four cases of carcinoma in a hyperplastic gland were mentioned by Clute and Warren.<sup>4</sup> No such simultaneous occurrence has been recorded in the large series of Wilson,<sup>5</sup> Herbst,<sup>6</sup> Simpson,<sup>7</sup> Brenizer and McKnight<sup>8</sup> and Crile.<sup>9</sup>

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From the Departments of Surgery and Pathology, Chesapeake and Ohio Hospital.

1. Coller, F. A.: Adenoma and Cancer of the Thyroid: A Study of Their Relation in Ninety Epithelial Neoplasms of the Thyroid, *J. A. M. A.* **92**:457-462 (Feb. 9) 1929.

2. Pemberton, J. de J.: Malignant Disease of the Thyroid Gland: A Clinical Consideration, *Ann. Surg.* **87**:369-377 (March) 1928.

3. Friedell, M. T.: Hyperthyroidism and Adenocarcinoma of the Thyroid, *Arch. Surg.* **43**:386-396 (Sept.) 1941.

4. Clute, M., and Warren, S.: The Prognosis of Thyroid Cancer, *Surg., Gynec. & Obst.* **60**:861-874 (April) 1935.

5. Wilson, L. B.: Malignant Tumors of the Thyroid, *Ann. Surg.* **74**:129-184 (Aug.) 1921.

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*(Footnotes continued on next page)*

It is obvious from these figures that the epithelium of the hyperplastic thyroid has extremely little, if any, tendency toward malignant degeneration. The reason for such behavior is not understood, and no attempt at explanation has been made. On the other hand, it is beginning to be understood why carcinoma does, although infrequently, arise in a hyperplastic gland. Clute and Warren<sup>4</sup> stated their belief that in such cases, carcinoma originates in a small adenoma within the hyperplastic gland. Similar evidence has been furnished by Goetsch.<sup>10</sup> By careful study of multiple blocks of tissue, he was able to demonstrate that miliary adenoma is considerably more frequent in the hyperplastic gland than was heretofore thought and to trace the origin of at least part of the carcinomas to these small adenomas. His observations were confirmed by Graham.<sup>11</sup> According to Graham, these small subcapsular scirrhous-like lesions of papillary or adenomatous structure infiltrate the adjacent tissue but apparently do not invade blood vessels. They do not seem to originate in adenoma. In concluding, Graham suggested that what has been considered a harmless lesion may have a malignant phase.

The case hereinafter reported forms, in our opinion, a connecting link between the early lesions described by Goetsch and Graham and the diffuse carcinoma in the hyperplastic thyroid, in which the histogenesis of the tumor is completely obscured.

#### REPORT OF A CASE

Mrs. O. W. R., a 55 year old white woman, was admitted to the surgical service on two occasions. The first time she was seen in June 1941, when a diagnosis of thyrotoxic heart disease with congestive failure was made. Even after adequate preparation, she was considered too poor a risk for operation, and she was allowed to go home. She returned after one month because of increasing nervousness, tremor of the hands, swelling of the ankles and a suffocating feeling in the right side of the chest.

She was somewhat emaciated. The skin was moist, and her eyes protruded slightly. She had a fine tremor of both hands. The heart was enlarged to the left. The blood pressure was 180 systolic and 118 diastolic; the pulse rate was

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7. Simpson, W. M.: A Clinical and Pathological Study of Fifty-Five Malignant Neoplasms of the Thyroid, *Ann. Clin. Med.* **4**:643-667 (Feb.) 1926.

8. Brenizer, A. G., and McKnight, R. B.: True Adenoma of the Thyroid Gland and Their Relation to Cancer, *Tr. Am. A. Study Goiter*, 1940, pp. 176-190.

9. Crile, G., Jr.: Hyperthyroidism Associated with Malignant Tumors of the Thyroid Gland, *Surg., Gynec. & Obst.* **62**:995-999 (June) 1936.

10. Goetsch, E.: Incipient Carcinoma Occurring in Exophthalmic Goiter and Originating in Adenoma, *Tr. Am. A. Study Goiter*, 1940, pp. 191-205.

11. Graham, A., in discussion on Goetsch.<sup>10</sup>

124 per minute. The liver and the spleen were enlarged, and the ankles were swollen. Electrocardiographic examination showed sinus tachycardia and a low T wave. The basal metabolic rate was + 53 per cent. The laboratory findings were essentially negative. The blood cholesterol content was 150 mg. per hundred cubic centimeters.

The diagnosis was hyperthyroidism complicating essential hypertension, enlargement of the heart and hyposystolic heart failure.

She was given a diet in which salt and fluid were restricted, and compound solution of iodine U. S. P. (Lugol's solution), digitalis and mercupurin were administered.

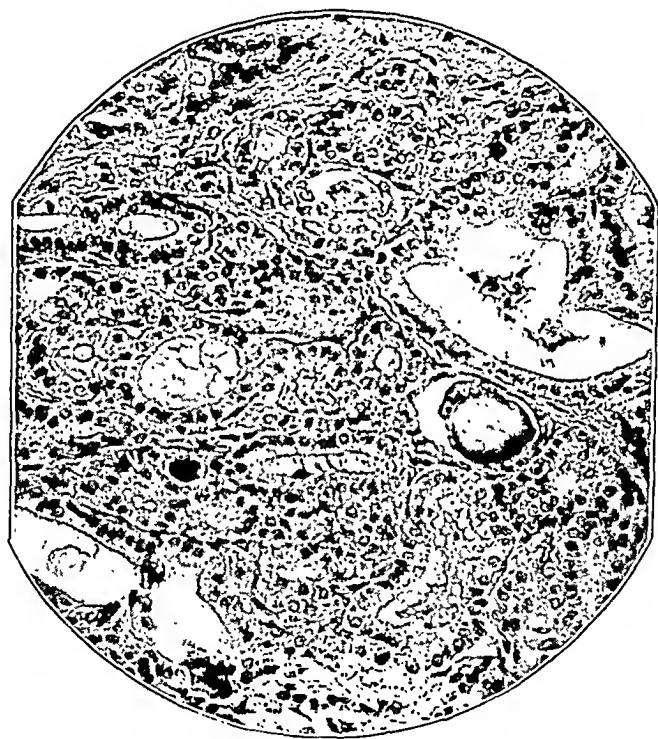


Fig. 1.—Photomicrograph showing an area of characteristic hyperplasia.

A week after admission she had an episode which was considered due to a pulmonary infarct. She recovered from this rather quickly, but her improvement on conservative therapy was not satisfactory. It was then felt that the symptoms of hyperthyroidism were definitely not secondary to the essential hypertension but that this was a combination of both thyroid and vascular disease and that the patient should have the benefit of thyroidectomy. Total thyroidectomy was performed on August 18. The operation did not present any particular difficulties.

The postoperative course was uneventful. The patient has since been seen on various occasions. At the time of writing, moderate hypothyroidism has developed. The cardiac decompensation was not noticeably improved by thyroidectomy, and at

the last examination, in December, it had taken a turn for the worse. There was no evidence of local recurrence of the thyroid carcinoma, nor was there regional or distant metastasis.

*Microscopic Examination.*—Both thyroid lobes were slightly enlarged. The capsule was somewhat thickened. The tissue was firm, with a dull dark brownish red beefy cut surface, which showed rather distinct small lobulation. In one lobe, a roughly spherical whitish gray firm scirrhous-like area with a softer yellowish center was located immediately beneath the capsule nearer to one pole. It measured 1.5 cm. in diameter.



Fig. 2.—Photomicrograph of papillary adenocarcinoma of the thyroid. This specimen is from the tumor inside the fibrous capsule.

*Microscopic Examination.*—The thyroid was hyperplastic, but to a varying degree. While large areas presented the characteristic picture of hyperplasia (fig. 1), in others the follicles were more regular, the epithelium lower, the colloid more abundant and acidophilic and less vacuolated. Lymphocytic infiltration was practically absent. The stroma was slightly increased.

Numerous blocks were taken from the area described before and cut at levels. The lesion appeared to be papillary adenocarcinoma of high differentiation (fig. 2).

The epithelium of the papillae formed one layer, and the cellular and nuclear structure was fairly regular. The tumor was completely surrounded by a thick fibrous capsule which contained small vessels and lymphatic tissue forming follicle-like aggregations. Round cells were also scattered loosely through the capsule. No mature or immature thyroid tissue was found inside the capsule. The papillary tumor invaded the capsule at numerous places and extended into the adjacent thyroid tissue, appearing there as a diffuse adenocarcinoma with narrow irregular, sometimes solid, glands. The cellular and nuclear structure, however, was, here too, fairly regular. In several places the lymphatic tissue and the small blood vessels of the capsule were invaded by the tumor (fig. 3).

*Diagnosis.*—The diagnosis was papillary adenocarcinoma in hyperplastic thyroid.



Fig. 3.—Photomicrograph of a tumor invading the lymphatic tissue and a vessel of the fibrous capsule.

#### COMMENT

We believe that the carcinoma originated in what probably was one of the small adenomas in the hyperplastic thyroid which were described by Goetsch.<sup>10</sup> In the present case, the carcinoma was already at a more advanced stage and had destroyed the original adenoma, but the complete encapsulation, the marked contrast to the thyroid gland proper and the absence of other areas of nodular involution surely support our opinion strongly.

Papillary overgrowth of epithelium, it is true, may occasionally be observed in hyperplastic goiters of long standing, but then such lesions are not so clearly separated from the thyroid tissue and surely are not malignant.

While one may hesitate to consider any papillary thyroid tumor malignant—in view of the regularity of the cellular pattern and the apparently good prognosis of many such lesions—we believe that the histologic criteria of malignancy of a thyroid tumor were fulfilled in the present case. Unquestionably, the papillary pattern represents the first step toward dedifferentiation of the thyroid epithelium. Together with the vessel-invading adenomas, the papillary tumors are classified by most observers in one group in contrast to the adenocarcinomas and undifferentiated tumors. Such a distinction is justified on clinical grounds, but there are no distinct histologic boundaries since the difference in pattern and extension are only expression of a varying degree of differentiation of what is basically always an adenocarcinoma arising from thyroid epithelium.<sup>12</sup> In our case, the tumor was papillary inside of the capsule but was a frank adenocarcinoma where it invaded the capsule and the thyroid proper. It is easy to imagine that with further spread of the tumor, sooner or later, depending on its rate of growth, all landmarks would become obliterated and that it would become entirely impossible to recognize whether the then diffuse adenocarcinoma originated in a small adenoma or in the gland tissue proper.

The importance of adenoma for the genesis of carcinoma is well established for the nodular goiter. It is beyond the scope of this paper to enter the much discussed argument: true adenoma versus nodular involution. The incidence of carcinoma in nodular (adenomatous) goiter is so much higher than in the smooth enlargements of the gland that a causal relation is certain.

The relative infrequency of adenoma in diffuse hyperplasia of the thyroid may account for the rarity of carcinoma in such glands, but it is probable that the adenoma represents the source of the carcinoma in all phases of goiter whether the morphologic equivalent of dysfunction is the hyperplastic or the nodular goiter.

In our case the hyperthyroidism was unquestionably due to the hyperplastic thyroid tissue and not to the tumor. That thyroid carcinoma itself may produce symptoms of hyperthyroidism was denied by Marine,<sup>13</sup> Eisen,<sup>14</sup> Pemberton,<sup>2</sup> Crile<sup>9</sup> and others, while Simpson<sup>7</sup> described cases of thyroid carcinoma producing hyperthyroidism and Friedell<sup>3</sup> reported that in 57 of 412 cases of thyroid carcinoma, a

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12. Broders, A. C.: *Surgical Pathology of the Thyroid Gland*, Tr. Am. A. Study Goiter, 1940, pp. 288-300.

13. Marine, D.: *Experimental Observations on the Effects of Administration of Iodine in Three Cases of Thyroid Carcinoma (Two Human, One Canine)*, Arch. Int. Med. **11**:288-299 (March) 1913.

14. Eisen, D.: *Malignant Tumors of the Thyroid: An Analysis of Seven Cases with a Study of the Structure and Function of the Metastases*, Am. J. M. Sc. **170**: 61-74 (July) 1925.

clinical diagnosis of hyperthyroidism was made, but only in a few cases could the thyroid itself be eliminated as the probable source of the thyrotoxic symptoms. That tumors of other endocrine glands may show secretory activity is well known. For the thyroid, the problem apparently remains unsettled for the time being.

Graham pointed out that small incipient carcinoma of the thyroid does not cause clinical symptoms and cannot be diagnosed before operation. According to him, removal by operation is sufficient, and irradiation is not indicated. We have not given radiation treatment to our patient, and she seems to be cured of the carcinoma. However, a single observation and the short time elapsed after operation do not permit of an opinion.

#### SUMMARY

A case of carcinoma of the thyroid arising in an adenoma in a hyperplastic gland is presented. The infrequent simultaneous occurrence of thyroid carcinoma and diffuse hyperplasia of the gland is discussed. The importance of miliary adenoma in the hyperplastic gland for the formation of carcinoma is stressed.

## INTRACRANIAL ARTERIAL ANEURYSMS IN THE CAROTID CANAL

### DIAGNOSIS AND TREATMENT

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Aneurysms of the cranial division of the internal carotid artery may arise (1) in the carotid canal and (2) within the cranium. There may or may not be differences in the signs and the symptoms of the two types, and the surgical attack which has been developed in the past few years may or may not be the same for both. The only symptomatic difference between aneurysms in these two locations is that many of those in the cavernous sinus produce disturbances of the trigeminal nerve while those of the intracranial portion do not. Nearly all aneurysms in the carotid canal are amenable to operative treatment with minimal risk; those in the intracranial division may or may not be curable, depending on the exact relation to the branches at the circle of Willis. I am concerned in this publication only with the arterial aneurysms in the carotid canal, particularly with the large ones. This location is also a favored seat for carotid-cavernous arteriovenous aneurysms with resultant pulsating exophthalmos, but these have been considered elsewhere. Rupture of the smaller arterial aneurysms in this region is indeed one source of the arteriovenous variety, and 1 of my cases has been included because this finding was present at necropsy. Most of the arteriovenous aneurysms in this position are of traumatic origin and are a common result because the torn internal carotid actually traverses the cavernous sinus.

### REPORT OF A CASE OF A LARGE ANEURYSM ARISING IN THE CAROTID CANAL

The patient was a rather frail woman 52 years of age. She was referred by Dr. Warde B. Allan, of Baltimore, on Nov. 19, 1941, with the probable diagnosis of an intracranial aneurysm (fig. 1). Dr. Frank Ford, the neurologist at Johns Hopkins Hospital, made the same diagnosis. The illness for which she was admitted to the hospital began three years before with diplopia which lasted a month and was said to have been corrected by glasses. However, it recurred periodically during the next three years. Four months before admission a tingling sensation in the right maxillary region and quickly thereafter numbness of the cheek and



forehead appeared. At the same time severe pain struck the right eye. Three weeks later, a sudden piercing headache developed in the right frontal region; this was accompanied by nausea and vomiting. On the following morning, the pain had concentrated in the right eye, and the right upper eyelid drooped (ptosis). The pains and the headache persisted, although for the last three weeks there was gradual improvement and for the last week they were barely noticeable. A spinal puncture had been made at the Gorgas Hospital at Ancon in the Panama Canal Zone six weeks before and was entirely negative.

The following findings were elicited on examination of the eyes by Dr. Frank Walsh, who also suggested an intracranial aneurysm: (1) total paralysis of all extraocular muscles on the right side (the third, fourth and sixth nerves); (2) exophthalmos of 4 mm. of the right eye; (3) enlargement and absence of

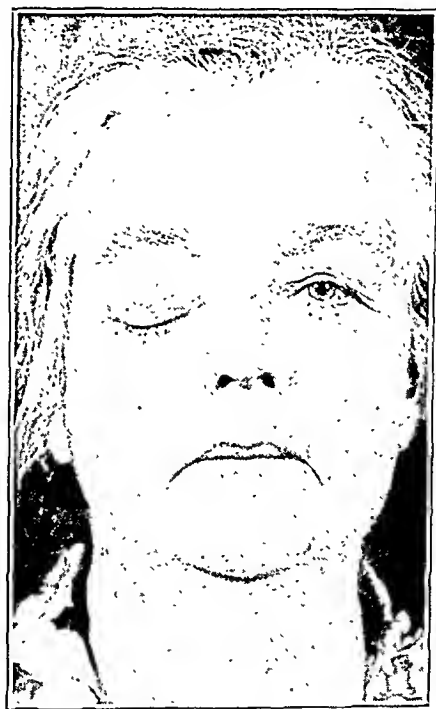


Fig. 1.—Photograph of the patient with a large carotid cavernous aneurysm showing complete ptosis and moderate exophthalmos.

reaction in the right pupil; (4) visual acuity, 20/50 for the right eye and 20/20 for the left; (5) small central scotoma on the right and normal fundi; (6) anesthesia of the first and second branches of the right trigeminus nerve; (7) destruction of the anterior and posterior clinoid processes on the right (no calcified shadows); (8) blood pressure, 192 systolic and 100 diastolic; negative Wassermann test.

In 1941, I reported the cases of 5 presumably cured patients with carotid aneurysms in the carotid canal. The cure was accomplished by trapping the aneurysm between a clip on the intracranial carotid and a total ligation in the neck. All of these patients were fairly young; the collateral circulation was adequate, and the aneurysms were small. I had feared that huge aneurysms of this type would probably be beyond hope of operative treatment, although I had not yet exposed one at operation. It was assumed that the intracranial portion

of the internal carotid artery would probably be hidden from view by the large intracranial protrusion of the aneurysm and furthermore that the possible collateral circulation through the circle of Willis would be compromised by the projection of the mass on the anterior and posterior communicating arteries. As is so frequently true, this supposition proved to be unfounded, and the problem, although not as simple as that of the smaller aneurysms because of other considerations, was solved without undue difficulties.

The collateral circulation was indeed demonstrated to be entirely inadequate by the Matas test, i. e., compression of the internal carotid artery in the neck. Total occlusion of this vessel could be tolerated less than a minute, and, therefore, ligation of the vessel without disastrous cerebral sequelae was precluded. However,

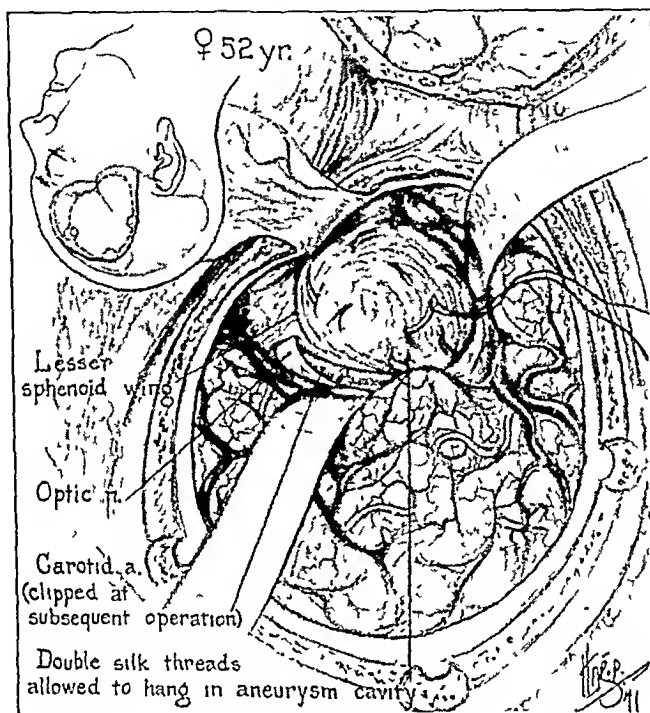


Fig. 2.—Operative sketch of carotid aneurysm in the cavernous sinus bulging far up into the temporal fossa. Since the Matas test indicated that the internal carotid could not be ligated without cerebral disturbances, a series of sutures was introduced into the aneurysm with the hope that they might cause a clot to develop and obliterate the aneurysm.

after partial occlusion of the internal carotid artery in the neck by a fascial band, the collateral circulation was found to be adequate, and four days later, the internal carotid was totally occluded intracranially by a silver clip and in the neck by a ligature (over the fascial band), thus trapping the aneurysm (fig. 3). Between the two ligatures there is only one sizable branch of the internal carotid artery, namely, the ophthalmic artery, and this, I believe, will not maintain the aneurysm. At least in none of the other 5 patients reported as cured has there been a suggestion of failure by subsequent signs or symptoms.

At the time of the final operation the internal carotid was simultaneously exposed intracranially and in the neck. When the silver clip was clamped on

the internal carotid artery within the cranial chamber, there was no visible effect on the violent pulsation of the aneurysm. Perhaps five minutes later the internal carotid was ligated with silk in the neck, and all pulsation in the aneurysm immediately stopped. It is probably worthy of note that the intracranial ligation was performed first. It perhaps made no difference which ligature was placed first since the time interval between the two ligatures was so short, but with a longer interval there is reason to believe that cerebral emboli may be prevented by ligating this artery intracranially first. It may or may not be important to place both ligatures almost simultaneously, but the thought occurred that an aneurysm not receiving blood would be smaller and therefore compromise the collateral circulation through the circle of Willis to a lesser degree. Recovery

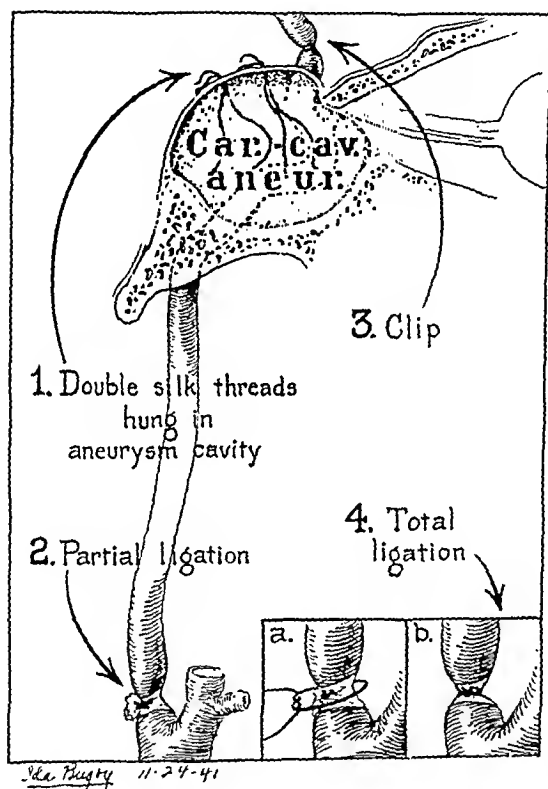


Fig. 3.—The final treatment of the aneurysm is indicated in this sketch. First the internal carotid was partially closed with a fascial band. Four days later, the internal carotid was clipped intracranially and ligated in the neck. A silk ligature was tied over the fascial band.

from the operation was uneventful and without any trace of cerebral involvement. It also should be added that at the time of the initial exposure of the aneurysm five days before these ligations, four double silk sutures of medium size were left dangling in the interior of the aneurysm (fig. 2). Each of the eight sutures was about 2 cm. in length. Owing to the thick capsule of the aneurysm, long curved needles could be passed through the aneurysmal wall and pulled until one end of the suture was left dangling inside. There was no evidence from the degree of pulsation of the aneurysm that they had induced a thrombus.

Perhaps in the smaller berry aneurysms they may be more effective and may possibly offer a means of curing those that cannot be extirpated or clipped at the neck of the sac.

The chronology of events in the surgical treatment of the aneurysm was: (1) exposure of the aneurysm intracranially on Nov. 24, 1941 (fig. 2); (2) partial ligation of the internal carotid in the neck on Nov. 25, 1941; (3) clipping of the internal carotid intracranially and total ligation in the neck on Nov. 29, 1941 (fig. 3); (4) discharge from the hospital on Dec. 22, 1941.

*Subsequent Course.*—The patient was examined by Dr. Walsh two months after the operation, on Jan. 28, 1942; at that time she was free from all symptoms and had been since operation. The vision in the affected eye had returned to 20/20 (from 20/50), and the central scotoma had disappeared. She could elevate the upper lid so that the entire pupil was exposed. The eye abducted 35 and adducted 7 degrees; it moved upward 2 and downward 2 degrees. Before

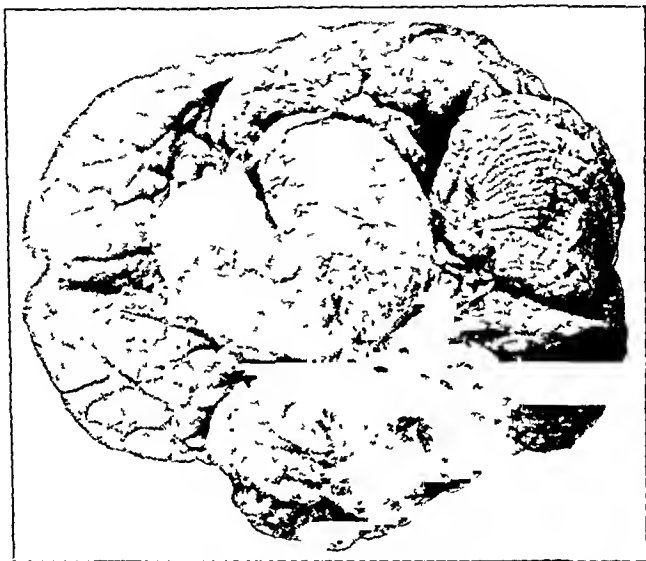


Fig. 4.—Postmortem specimen of huge bilateral carotid aneurysms in the carotid canal (previously reported).

operation the eyeball had been fixed. The exophthalmos had not diminished. She was then returning to her home in Panama.

Heretofore, an interval of three to four weeks had been allowed between the partial and the total closure of the internal carotid artery. The advent of facial weakness on the contralateral side from a small extradural hemorrhage necessitated reopening the wound, and for that reason it was reluctantly determined to close the carotid at the same time (the Matas test then indicating that the circulation was adequate).

#### COMMENT

In a recent review of 108 arterial aneurysms of the brain that came to operation or necropsy, 9 (8.3 per cent) were in the carotid canal; in 1 case the condition was bilateral (fig. 4). From the literature, 27 additional cases have been collected, in 3 of which the condition was

Author	Date	How Proved	Size	Unilateral or Bilateral	Patient		Duration of Symptoms	Headache	Pain	Paralysis of Third Nerve	Paralysis of Fourth and Sixth Nerves
					Age, Yr.	Sex					
Blane.....	1800	Neeropsy	.....	Bilateral and symmetric	..	..	.....	.....	.....	.....	.....
Holmes.....	1861	Neeropsy	Size of a small nut	Unilateral	16	M	3 mo.	General	Over the left eye	Complete	Complete
Adams.....	1869	Neeropsy	Size of a walnut	Unilateral	56	M	5 mo.	.....	Right temporal	Complete	Complete
Romberg.....	1853	Neeropsy	Double normal size of carotid	Unilateral	57	M	10 yr.	.....	Facial neuralgia	None	None
Hutchinson.....	1875	Neeropsy	Size of a bantam's egg	Unilateral	50	F	11 yr.	Periodic	Throbbing temple	Partial; later, complete	Complete in the sixth
Bramwell.....	1886	Neeropsy	3 in. (7.6 cm.)	Unilateral	31	M	6 yr.	.....	.....	.....	.....
Dempsey.....	1886	Neeropsy	$\frac{3}{4}$ in. (1.9 cm.) in diameter	Unilateral	22	F	.....	None	+ From ophthalmic aneurysm	None	None
Czermak.....	1902	Neeropsy	5.5 cm.	Unilateral	..	..	8 yr.	.....	.....	Complete	Complete
Czermak.....	1902	Neeropsy	Size of a mandarin	Unilateral	61	M	8 yr.	+ Right frontal	.....	Complete	Complete
Reinhardt.....	1913	Neeropsy	4.5 by 4 cm.	Unilateral	41	M	0 yr.	Severe	In the left part of the forehead and the left eye	Complete	Complete
Nettleship..... (reported by Beadles)	1907 (1889)	Neeropsy	4 cm.	Unilateral	61	F	10 yr.	.....	In the nose	Complete	Complete
Huer and Dandy (case 1)	1916	Neeropsy	3.5 by 2 by 2 cm. and 8 by 7 by 7 cm.	Bilateral	29	M	5 yr.	Violent	In the left eye and the head	Complete	Complete
Cushing..... (reported by Viets)	1918	Operation; decompression	Size of a walnut	Unilateral	26	F	7 wk.	+	Sudden in the right side of the head	Complete	Complete
Magnus.....	1927	Operation	Size of a chestnut	Unilateral	69	M	3 mo.	None	Constant facial neuralgia	None	Abducens only
Bozzoli.....	1937	Neeropsy	Large	Bilateral	59	M	3 mo. (following trauma ?)	None	.....	None	None
Jefferson.....	1937	Operation	Very large in drawing	Unilateral	60	F	5 yr.	Dull left sided	.....	Complete	Partial in the sixth
Robinson..... (reported by Beadles)	1937	Neeropsy	1 inch (2.5 cm.) diameter	Unilateral	..	..	.....	.....	None	None	None
Fineher.....	1938	Colloidal thorium dioxide	Small	Unilateral	35	M	5 mo.	+ Vertical	+	Complete	Abducens palsy
Jefferson..... (case 1)	1938	Operation for trigeminal neuralgia	Large	Unilateral	65	F	18 yr.	+	Constant trigeminal neuralgia and pain in the head	None	Complete

# Carotid Canal Reported in the Literature

Paralysis of Fifth Nerve	Visual Loss	Exophthalmos	Other Signs and Symptoms	Intra-cranial Pressure	Diagnosed Correctly	Treatment	Result	Rupture	Comments
.....	.....	.....	.....	None	No	.....	.....	.....	
First branch	Blind on affected side	.....	Giddiness	None	No	None	Dead	No	Partly filled with clot; center open; thought to be due to endocarditis
First and second branches	Blind on affected side	.....	Giddiness; cornea ulcerated	None	No	None	Dead	No	Partly filled with clot; center open
Neuralgia	None	.....	Giddiness	.....	No	None	Dead	No	Patient had only trigeminal neuralgia
All branches	None	.....	"Beating under the ears"	Probably	Yes	None, but it was proposed to ligate the carotid	Dead	No	Aneurysm removed and preserved in the museum of the Royal College of Surgeons; thought to be solid; calcified walls
.....	Bitemporal hemianopia	.....	.....	Probably	No	None	Dead	No	Protruded into cranial cavity
None	.....	+ From opb. thalamic aneurysm	Principal symptoms from opb. thalamic aneurysm	None	No	Common carotid tied	Dead	No	Patient had intracranial carotid aneurysm and one of the ophthalmic artery also
All branches	.....	.....	.....	Present	No	None	Dead	Yes	
All branches	Blind on affected side from keratitis	None	Syphilis; keratitis first symptom	Probably	No	None	Dead	+	Abducens palsy 6 yr. before advent of third nerve change
All branches	Blind on affected side	+	.....	Present	No tumor diagnosed	None	Dead	No	Photograph of enormous aneurysm; much of the aneurysm filled with firm clot
Probably not involved	Blind in one eye	+	Exophthalmos; bleeding from nose repeatedly	Present	No	None; ligation suggested	Dead	Yes; into the nose	Another small aneurysm was in the neck; patient died of nasal hemorrhage; specimen in museum
All branches	Blind in the left eye; temporal hemianopia on the right	+	.....	Marked	No; but suggested as a possibility by Dr. H. M. Thomas	None (decompression)	Dead	No	Marked long linear shadows in the brain; destruction of sella (first case with roentgen changes)
First and second branches	None	None	Discomfort in the neck; dizziness; vomiting	Present	No	None	Died 1 yr. later	?	Died suddenly; no autopsy
All branches; hypo-esthesia	None	.....	.....	None	At operation for trigeminal neuralgia	Internal carotid ligated in the neck	.....	.....	Encountered and opened during operation for tic douloureux (temporal route)
None	Visual acuity 1/10 for the left eye; 2/10 for the right eye	None	Syphilis; calcification alongside the sella	None	No	None	Dead	No	
All branches	Visual acuity, 6/60	+	Weakness on the right side of the body; erosion of the wing of the sphenoid; faint roentgen shadow; the sella not eroded	Present	No	None	Dead	No	Patient died 8 wk. later following increase in hemiplegia; "almost completely" thrombosed
None	None	.....	None	None	No	None	Dead	No	Recorded in museum; Bendles stated that there was no clinical evidence of the existence of an aneurysm
None	None	.....	.....	None	Yes	Clipping carotid intracranially after tying in neck	Well	No	
Possibly (alcohol injection given)	None	None	Calcification developed in aneurysm; several years later there was periodic bleeding from the nose; blood pressure, 175/100	None	No	None	Died 14 yr. later	.....	Began with sudden severe pain in the head; vomiting; coma for 2 or 3 days

*Aneurysms of the Internal Carotid in the Carotid*

Author	Date	How Proved	Size	Unilateral or Bilateral	Patient		Duration of Symptoms	Headache	Pain	Paralysis of Third Nerve	Paralysis of Fourth and Sixth Nerves
					Age, Yr.	Sex					
Jefferson..... (case 3)	1938	Operation	Large	Unilateral	61	F	20 yr. (head-ache)	+	.....	Complete	Complete
Jefferson..... (case 8)	1938	Operation	Small	Unilateral	61	F	3 mo.	+ Right frontal	+ Behind the right eye	Complete	Complete
Jefferson..... (case 16)	1938	Necropsy	Large	Bilateral	72	F	1 mo.	+ Left	Trigeminal	Incomplete on the left	Incomplete on the left
Sands and Hyman	1938	Necropsy	4.5 by 4 by 3.5 cm.	Unilateral	24	F	10 yr.	Present at end	.....	.....	Abducens palsy
Dandy (case 2)...	1939	Operation	Small	Unilateral	28	F	5 mo.	+ Left frontal	In the left eye	Complete	Complete in the fourth but not in the sixth
Dandy (case 3)...	1939	Operation	Small	Unilateral	36	M	8 mo.	+ Left frontal	In the left eye	Partial	None
Dandy (case 4)...	1939	Operation	Small	Unilateral	37	F	5 yr.	+ Right frontal	In the right eye	Complete	None
Reichert.....	1938	Colloidal thorium dioxide	Large	Unilateral	50	M	9 yr.	+ Present 2 to 3 yr.	+ In the right part of the forehead	Complete	Complete
Dandy (case 5)...	1941	Necropsy	Size of a hazelnut	Unilateral (2 lesions)	53	M	None from arterial aneurysm until rupture	.....	.....	.....	.....
Kosic.....	1941	Colloidal thorium dioxide	Small	Unilateral	42	F	3 wk.	.....	.....	Complete	Complete
Krayenbühl.....	1941	Colloidal thorium dioxide	4 by 3.5 cm.	Unilateral	21	F	8 mo.	+	Severe in the left part of the forehead	None	Complete in the sixth
Krayenbühl.....	1941	Operation (colloidal thorium dioxide negative)	Walnut size	Unilateral	44	M	18 mo.	+	+ In the left eye and the left part of the forehead	Complete	Complete
Werner, Blake-more and King	1941	By wiring (roentgenograms)	Very large	Unilateral	17	F	6 yr.	Generalized and severe	In the right eye and temple	None	Diplopia without ptosis
Dandy (case 6)...	1942	Operation	Small	Unilateral	24	M	22 yr.	+ Left frontal	In the left eye	Complete	Partial
Dandy (case 7)...	1942	Operation	Small	Unilateral	20	M	3 mo.	+ Right frontal	In the right eye	Complete	Complete
Dandy (case 8)...	1942	Operation	Huge	Unilateral	52	F	4 yr.	+ Right frontal	In the right cheek	Complete	Complete

Paralysis of Fifth Nerve	Visual Loss	Exophthalmos	Other Signs and Symptoms	Intra-cranial Pressure	Diagnosed Correctly	Treatment	Result	Rupture	Comments
All branches	None	.....	Began with sudden terrific pain in the left temple; diplopia for a few days (3 yr. earlier); blood pressure, 135/90	?	Yes	None	Living 5 yr. later	No	Exposed through decompression
First branch	None	None	Erosion of the sella	None	Yes	None	Living 6 yr. later	No	
Hypoalgesia on the whole left side	Loss to visual acuity of 2/24 in each eye	None	Erosion of the sella	None	Yes	None	Dead	No	Patient died of coronary occlusion; the left aneurysm was five or six times as large as the right
Anesthesia of the cornea	None	.....	Double vision; convulsions; attacks of mental confusion	Present	No	None	Dead	Yes	Projected into the brain
None	Vision reduced on the affected side	None	.....	None	Yes	Internal carotid ligated intracranially in the neck	Living 5 yr.	+	Aneurysm broke through the dura; small protrusion intracranially alongside the carotid
Tickling sensation in the neck	Blurring in the left eye; visual acuity 20/30 for the left eye and 20/120 for the right	None	.....	None	Yes	Aneurysm trapped between ligatures	Living 3½ yr.	No	Aneurysm broke through dura alongside the intracranial part of the carotid
None	Visual acuity 20/50 for the right eye and 20/25 for the left	None	.....	None	Yes	Aneurysm trapped between ligatures	Living 3½ yr.	Probably	Aneurysm broke through dura alongside the intracranial part of the carotid
None	Visual acuity 5/10; small central scotoma	+	Noise in the ear on the same side; no pulsation in exophthalmus; papilledema	?	Yes	Partial ligation of the carotid with fascia	Well	No	Improvement after operation (3 weeks)
.....	Not from arterial aneurysm	+ Not from arterial aneurysm	All signs of pulsating exophthalmos	None	No	Attempted closure of internal carotid	Dead	No	Operation for carotid-cavernous arteriovenous aneurysm; cause found at necropsy to be rupture of two small arterial aneurysms; artery tore, death resulting
None	None	None	.....	None	Yes	None	Living	No	
None	None	+	Some erosion of the sella; double vision first symptom	None	Yes	Ligation of the carotid	Well	No	Two years later strabismus gone and the patient felt well
First and second branches	Blind on affected side	+	.....	None	Yes	Ligation of the carotid	Well	No	Three weeks after operation extraocular palsies much improved and anesthesia of the face reduced
Hyperesthesia of all branches	Eventually blind	+ 5 mo.	Bruit heard; erosion of the sella, the orbit and the sphenoid; Simmonds' disease; amenorrhea	Probably	Yes	Wiring (30 ft. [914.4 cm.]); both common carotids tied	Living 22 mo.	No	
None	Visual acuity 10/400 for the left eye and 20/15 for the right	None	Small dense calcification in the cavernous sinus	None	Yes	Aneurysm trapped between ligatures	Living 2¾ yr.	Probably	Third nerve palsy persisted since age of 2 yr.; aneurysm confined to sinus
None	None	None	.....	None	Yes	Aneurysm trapped between ligatures	Living 3¾ yr.	Probably (bloody spinal fluid)	Large nut-sized aneurysm broke through dura alongside the carotid
All branches (partial)	Visual acuity, 20/50 for the right eye and 20/20 for the left	+ 4 mm.	The sella destroyed; central scotoma on the right	Present	Yes	Aneurysm trapped between ligatures after partial ligation in the neck	Living 2 mo.	No	One of the enormous aneurysms pushing far upward into the temporal lobe



bilateral. The total number of cases therefore is 35, and the total number of aneurysms, 39. The 4 bilateral cases in the literature were reported by Blane (1800), Heuer and Dandy (1916), Jefferson (1938) and Bozzoli (1937). When bilateral, aneurysms may be symmetric (Blane), nearly symmetric (Bozzoli) or markedly asymmetric (Heuer and Dandy, Jefferson).

Jefferson (1938), in an excellent paper, reported 17 cases, but only 6 of these (including 2 in 1 patient) were authenticated; the remainder were assumed to be cases of aneurysm in the carotid canal because of signs and symptoms. But important as are the subjective and objective disturbances, they are by no means pathognomonic either of aneurysms or of the exact location of the lesion, i. e., whether in the carotid canal or intracranial. Two of Jefferson's aneurysms diagnosed by angiograms were clearly intracranial because they extended to the circle of Willis.

There are three methods by which the aneurysm and its exact position can be determined: (1) by necropsy; (2) by operation, and (3) by angiograms. A fourth method should probably be included, viz., roentgenograms of wire inserted into the aneurysm (Werner, Blakemore and King's case). There may be occasional calcifications which are adequately demonstrated by roentgen examination, but in most cases, even with the knowledge that calcifications are present, one is still left in doubt whether the lesion is a tumor or an aneurysm. For example, it is possible that 2 of the aneurysms reported by McKinney, Acree and Soltz may have been in the carotid canal, but no differentiation was made between these two subdivisions of the carotid, and it is impossible to make the determination from their roentgenograms; moreover, the writers placed them in the cranial chamber. The first description of the curved linear intracranial roentgen shadows that are almost pathognomonic of the calcified walls of aneurysms was reported by Heuer and myself in 1916 (case 1, fig. 5). Although neither Heuer nor I was aware of their significance at the time, their import was recognized by Dr. H. M. Thomas, then professor of neurology at the Johns Hopkins University School of Medicine, and the suggestion of an aneurysm was made by him and is so recorded in the history. Shadows of similar character are shown in the plates presented by Sosman and Vogt (1926) and McKinney, Acree and Soltz (1936). In 1 other case (case 6) in my series, a small dense irregular calcification in the carotid canal could leave no doubt concerning the diagnosis, especially when connected with the history. In Bozzoli's case, bilateral shadows alongside the sella turcica were of similar character.

Since the advent of angiography by Egas Moniz in 1933, intra-arterial injections of colloidal thorium dioxide have demonstrated many intracranial aneurysms. Beautiful examples of those in the carotid canal have been reported by Fincher (1938), Reichert (1939), Kraysenbühl

(1941) and Kasic (1941). A second aneurysm of Krayenbuhl failed to show in an arteriogram and was disclosed at operation. The demonstrations of aneurysms of this type at operation have been made by Cushing (1918—reported by Viets), Magnus (1927), Jefferson (1938)—4 cases—and me—6 cases. There can be no uncertainty about the diagnosis at operation, for the aneurysms pulsate, and blood can be aspirated from them if there is any doubt. Magnus opened an aneurysm while operating for trigeminal neuralgia, but the patient survived after the aneurysm had been packed and the internal carotid artery ligated in the neck. Cushing exposed one through a decompression opening. In 1 of

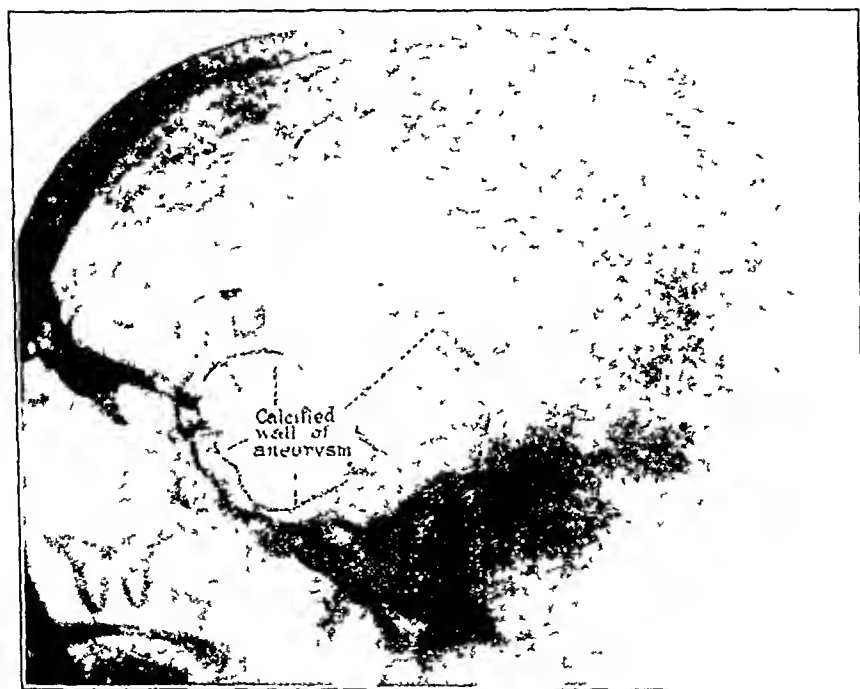


Fig 5—Calcifications in the aneurysms shown in figure 4 Note their linear character and one whorl; also, destruction of the sella turcica.

Jefferson's cases, the aneurysm was exposed during a trigeminal operation, and the patient lived fourteen years. In his other 3 cases, the aneurysms were found when the clinically localized lesions were explored. In all of my 6 operative cases, the patients were operated on with the impression that the lesions were aneurysms and with surgical attack in mind.

Aneurysms in the carotid canal vary in size, like those located intracranially, from the so-called small berry aneurysm to those the size of an orange. Some are localized projections from the wall of the artery; others are dilatations of the whole arterial trunk.

According to signs and symptoms, aneurysms of the carotid canal fall into three types: (1) those giving palsies of the extraocular muscles; (2) those giving trigeminal neuralgia and corresponding sensory loss, and (3) those in which types 1 and 2 are combined. By far the most important manifestations of an aneurysm in this region are palsy or paralysis of the third nerve and periodic severe pain in the affected eye or frontal region. These disturbances are equally present with intracranial aneurysms of the internal carotid or even of the posterior communicating artery. But when to this pain and paralysis is added involvement, whether subjective or objective or both, of the first and second branches of the trigeminal nerve (eventually of all three branches), the diagnosis of an aneurysm, and that one in the carotid canal, is almost absolute. Usually paralysis of the fourth and sixth nerves coexist. In Czermak's case palsy of the abducens antedated that of the third nerve by six years (in his case anesthesia of the cornea [fifth cranial nerve] also antedated involvement of the third nerve by the same time). Dural tumors of the lesser wing of the sphenoid and neuritis of the third nerve also may give identical objective findings, but with both of these conditions the severe attacks of pain in the eye and the frontal region are absent. Pain of this character and location has been perhaps the most consistent subjective complaint in all of the recorded cases. A sudden severe pain is always suggestive of vascular expansion or rupture.

Since these aneurysms lie on the gasserian ganglion, it is expected that trigeminal neuralgia, probably more or less continuous, and eventually sensory loss should be present. Actually, however, in 10 cases these subjective and objective disturbances were absent or not noted. Their absence therefore does not militate against the diagnosis of an aneurysm in the carotid canal, but their presence is all important. Romberg's (1853) patient, who had 1 of the smallest aneurysms reported, had only facial neuralgia; the patients of Magnus (1927) and Jefferson (1937) had this type of neuralgia plus palsy of the abducens. Jefferson proposed subdivision of aneurysms in the carotid canal into three further types: (1) posterior; (2) middle, and (3) anterior, i. e., corresponding with the three positions of the lesion in the carotid canal. Under the posterior type of aneurysm he placed those with involvement of all three branches of the trigeminus and palsies of all the extraocular muscles. With the middle type the third branch of the trigeminus is spared, and with the anterior type only the first branch of the trigeminus is involved. However, there appears to be little point in this finer classification. The greatest involvement of nerves is more an index of the size of the aneurysm.

Loss of vision is an important and common subjective and objective disturbance. It is of course due to direct pressure of the bulging aneurysm on the optic nerve or on the nerve through the interposed carotid artery as in 1 of my cases (case 8) in which there was only a

central scotoma. Eventually there may be blindness in the eye on the affected side. Occasionally, as in 1 of my cases, the aneurysm may enlarge sufficiently to attack the optic chiasm and produce hemianopia in the other eye. When one sees the enormous size of many of these aneurysms, it is surprising that vision is retained so long. It is the tightly attached dura at the anterior part of the middle fossa that protects the actual contact with the optic nerve until the size of the aneurysm grows excessive and finally compresses it.

At times papilledema results from intracranial pressure as the aneurysm grows upward into the cranial chamber. Both eyegrounds may be similarly affected, or there may be primary optic atrophy on the affected side and papilledema on the other side.

The very nature of aneurysms, i. e., their being due to defective arterial walls, predisposes them to rupture, and since a high percentage—at least 75 per cent—are of congenital origin, frequently the rupture occurs in the early years of life. Aneurysms in the carotid canal are less susceptible to rupture than those within the cranial chamber because they are covered by the firm layer of dura which expands slowly. This accounts for the long duration of symptoms in so many instances. However, they are by no means immune to this termination. Four deaths resulted in this collected series from this cause—the rupture taking place into the cranial chamber. In 3 of my operative cases, the rupture had probably occurred alongside the carotid (from small intracranial extensions), and the point of rupture had healed owing to the contact with the carotid artery. In 1 of my cases (case 2) two separate small aneurysms had ruptured into the cavernous sinus and produced an arteriovenous aneurysm (pulsating exophthalmos). This is one of the important causes of this remarkable lesion; it may occur spontaneously or be induced by trauma. In this case the existence of the arterial aneurysm as the underlying cause was recognized only at necropsy. In Nettleship's case repeated ruptures had occurred into the nose, death finally resulting.

Exophthalmos was noted in 9 cases, including the case reported here. This can occur only with the large aneurysms which have eroded the walls of the sphenoid fissure and have therefore broken through into the orbit. Pulsation of the eyeball was noted but rarely in spite of the violent pulsation of these aneurysms; doubtless it was missed in some instances. Dempsey's case is noteworthy because in it there was an aneurysm of the ophthalmic artery in addition to the diffuse enlargement of the internal carotid artery ( $\frac{3}{4}$  inch [1.9 cm.]) in the canal.

Bruit was noted only in the case reported by Werner, Blakemore and King. Hutchinson was skeptical of reports of bruits with intracranial aneurysms and concluded that a bruit was present only with the arteriovenous variety—then termed aneurysm by anastomosis. In none of my

cases was a bruit detected. It does occur, but only rarely, and is hardly worthy of consideration in differential diagnosis.

That a spontaneous cure of an aneurysm of this type ever occurs is doubtful, though perhaps possible. Frequently the aneurysm is partially filled with a firm old thrombus that is laid down in layers. Hutchinson noted that the aneurysm in his case was "almost entirely" filled with thrombus; however, the specimen was not opened, and his deduction was made by probing. Jefferson stated that 1 of his large aneurysms was "almost completely" thrombosed. Many aneurysms are indeed almost completely filled with thrombus, but a central channel is usually patent and is in communication with the lumen of the artery, and they still remain active aneurysms. In 1 of Krayenbühl's cases, the internal carotid and the middle cerebral arteries were completely thrombosed (hemiplegia resulting). It appears probable that this may have been a case of complete thrombosis and cure of the aneurysm, but the patient survived, and no pathologic report was therefore in evidence.

The ages of patients at the time of operation, death or disclosure of the aneurysm run fairly evenly according to decades. Only 2 were under 20, although several of those in the succeeding decade had their origin before 20. In 1 of my cases (case 6), the aneurysm ruptured at the age of 2 years. Eight aneurysms occurred in the third and sixth decades; 6, in the seventh; 4, in the fourth; and 3, in the fifth. The oldest patient was 72 (Jefferson). Sixteen patients were male and 16 female. Twenty of the aneurysms were of the large type that protrudes upward into the cerebral chamber; many of these caused intracranial pressure.

The duration of symptoms varies considerably; 18 patients (over 50 per cent) had symptoms over three years; 9 had symptoms nine years or more; 3 lived eighteen, twenty and twenty-two years, and at the time of writing, 1 (case 6) is still living after twenty-five years. In several cases, however, the course was more fulminating, lasting a few weeks or months.

The fact that 13 of these aneurysms were actually disclosed at operation testifies to the great progress in neurosurgery in recent years. A few were accidental disclosures, 2 (Magnus and Jefferson) being found during operation for trigeminal neuralgia by the temporal route. Magnus had the terrifying experience of opening the aneurysm but was able to pack the opening and tie the internal carotid artery in the neck. Despite the advanced age of the patient (69 years), the ligation caused no ill effects. The extradural approach to the gasserian ganglion of course reduces the hazards of a ruptured aneurysm in this position.

The disclosure of aneurysms by angiography has attained a great vogue since its introduction by Egas Moniz, and viewed superficially, the results appear to be remarkable. Certainly the roentgenograms depict the lesion beautifully both in diagnosis and localization, but from a

practical point of view, I consider its use inadvisable. It is not a procedure without risk. Cerebral thromboses were reported by Ekström and Lindgren in 60 per cent of the brains examined after death. These may or may not cause symptoms at the time, but they certainly are a potential cause of epilepsy. Moreover, the colloidal thorium dioxide is a permanent deposit in the reticuloendothelial system. There is no reason to inject it when the signs and symptoms clearly indicate the site of a lesion which should be exposed at operation. This statement holds true for all aneurysms in the carotid canal, where the localizing disturbances are so pathognomonic of the site of the lesion and clinical judgment is almost adequate to identify the character of the lesion. If it was a matter of diagnosing a hopeless type of lesion and thus avoiding an operation, it might be a procedure of merit, but all the aneurysms in this group are operable and should be operated on. In 1 of Krayenbühl's cases, the angiogram did not disclose the lesion which was subsequently found at operation. Patients are certainly better without it!

Of the 7 patients operated on there was 1 who died—a mortality rate of 14 per cent. The death occurred in a case in which operation was done for a carotid-cavernous arteriovenous aneurysm, and at necropsy the cause of the arteriovenous aneurysm was found to be rupture of two small arterial aneurysms in the carotid canal. Death was due to rupture of an oversized arteriosclerotic artery during the application of a silver clip that was too small. In over 20 closures of the carotid intracranially by this method, this was the only accident. The other 6 patients were cured, the longest period after operation being three and one-half years.

#### SUMMARY

The case of a presumably cured patient with a large aneurysm of the internal carotid artery arising in the carotid canal and extending into the cranial chamber is presented.

The differential diagnostic signs and symptoms are emphasized.

The surgical attack previously employed for the smaller aneurysms, viz., trapping the aneurysm by ligating the internal carotid artery intracranially and in the neck, was applied with equal success to 1 of enormous size after forcing adequate collateral circulation through the circle of Willis by preliminary partial ligation of the internal carotid in the neck.

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## SURGICAL SIGNIFICANCE OF EPIPLOIC APPENDAGES

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Epiploic appendages are flattened projections of serosa-enclosed fat found along the colon from the cecum to the lower portion of the sigmoid, attached chiefly along the anterior taenia coli. Their size varies from a few millimeters to several centimeters. Blood is supplied by means of a single circular artery and vein, forming an arcade which extends into the tag. These appendages are present after the fifth to the seventh fetal month, although they are often overlooked if the patient is young or thin. Their function is not definitely known. It is likely that they act as a depot for fat, as a protective mechanism in peritoneal infection and as a cushion to the colon and its increasingly more solid contents.

It is generally acknowledged that epiploic appendages frequently undergo torsion, infarction and calcification; that they often produce symptoms closely simulating abdominal conditions requiring operation is appreciated less widely, and that they occasionally initiate pathologic states incompatible with health or even life is generally overlooked. We recently reviewed the instances of pathologic epiploic appendages reported in the literature and those encountered at the Mayo Clinic over a period of thirty-five years. We wish to summarize those cases in which symptoms definitely related to the appendages were present and to stress the significance of diseased epiploic appendages as a factor in acute and chronic abdominal conditions.

The pathologic conditions encountered included torsion, thrombosis and infarction; cystic, hyaline or calcareous degeneration; simple necrosis; gangrene; inflammation; hyperplasia and secondary carcinomatous implantation. Torsion undoubtedly initiates the great bulk of pathologic changes, but not all abnormalities of the epiploic tags should be classified under this heading. The general insistence on this term in the literature is misleading. In our series of cases, although torsion fre-

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quently could be assumed, actual twisting of the pedicle was not often demonstrable.

From the clinical standpoint, a practical classification of abnormal epiploic appendages would segregate the intra-abdominal from the hernial appendages and the free from the attached appendages. But this form of classification would chiefly distinguish between the symptomatic group and the asymptomatic or incidental group. We have employed such a method of classification. Both groups are separated into those appendages involved by primary pathologic processes and those secondarily involved. Our classification is as follows:

A. Symptomatic conditions (of intra-abdominal appendages):

1. Primary disease of an appendage
2. Secondary involvement of an appendage

B. Asymptomatic or incidental conditions

1. Of intra-abdominal appendages
  - a. Primary involvement of an appendage
  - b. Secondary involvement of an appendage
  - c. Free or detached appendages
2. Of intrahernial appendages

#### REVIEW OF THE LITERATURE

Epiploic appendages were first described in 1543 by Vesalius.<sup>1</sup> Littré,<sup>2</sup> in 1703, reported finding an epiploic appendage as a free foreign body in the peritoneal cavity of a cadaver. Similar findings were reported at later dates by Virchow,<sup>3</sup> Cruveilhier<sup>4</sup> and Laveran.<sup>5</sup> Hunt<sup>6</sup> placed Tomellini's case first in his review of cases of intra-abdominal torsion reported in the literature. Tomellini<sup>7</sup> demonstrated at necropsy in a case in which cardiac paralysis had caused death an epiploic appendage with a pedicle which had undergone true torsion around its long axis.

Analysis of the literature reveals that interest has been mounting in recent years on the subject of intra-abdominal torsion of epiploic appendages. To date, however, true symptomatic intra-abdominal torsion rarely has been diagnosed preoperatively. In fact, the only report of a

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1. Vesalius, A., cited by Harrigan, A.: Torsion and Inflammation of the Appendices Epiploicae, *Ann. Surg.* 66:467-478, 1917.

2. Littré, cited by Davis.

3. Virchow, R., cited by Hunt.<sup>6</sup>

4. Cruveilhier, J., cited by Hunt.<sup>6</sup>

5. Laveran, cited by Hunt.<sup>6</sup>

6. Hunt, V. C.: Torsion of Appendices Epiploicae, *Ann. Surg.* 69:31-46 (Jan.) 1919.

7. Tomellini, cited by Hunt.<sup>6</sup>

case in which the diagnosis was made before operation was reported by Babcock.<sup>8</sup> Insidious in character, diseased epiploic appendages can produce symptoms which simulate appendicitis, cholecystic disease, intestinal obstruction and other abdominal conditions.

Of the cases of intra-abdominal torsion of epiploic appendages collected from the literature by Hunt and of those reported by him, in 12, symptoms and conditions requiring operation were present which caused divergent preoperative diagnoses to be made as follows: appendicitis in 3, appendicitis and cholecystitis in 2 and, in 1 case each, diverticulitis, intestinal paralysis, tumor of the sigmoid, intestinal obstruction and disease of the left fallopian tube and ovary. In 2 of the 12 cases, diagnosis was not made; the only pathologic finding to explain the symptoms in these cases was torsion of the epiploic appendages.

Of the cases reviewed by Fiske<sup>9</sup> in 1936, in 21, the condition was symptomatic, and intra-abdominal torsion, infarction or inflammation was the only lesion discovered at operation. The preoperative diagnosis had been appendicitis in 10, torsion of an ovarian cyst in 3 and, in 1 each, torsion of an epiploic appendage, diverticulitis and Meckel's diverticulum. Diagnosis was not made in 5 cases.

Pines and associates<sup>10</sup> recently reported 7 cases of intra-abdominal torsion and hemorrhagic infarction of epiploic appendages. A preoperative diagnosis of appendicitis was made in 4 instances and, in 1 case each, diverticulitis, sigmoiditis with perforation and abscess of the abdominal wall. At operation, torsion of the epiploic appendages was found in 4 cases, and in 3, infarction was the only lesion found.

Nine cases of symptomatic primary lesions of epiploic appendages have been collected from the literature in addition to those mentioned, bringing the total to 49. Abstracts of the 9 cases are included in table 1.

Of the 49 cases reviewed in which symptoms were present, in 39 acute abdominal symptoms were present at the time of operation. In 10 of these 39 cases, a history of chronic symptoms also was present; in the 10 remaining cases, the symptoms of abdominal pain were chronic. Abdominal pain was a constant feature in all cases, and the location of the pain usually depended on the site of the lesion. The pain was situated in the left lower quadrant of the abdomen in 22 cases, in the right lower quadrant in 17 and in the epigastrium in 3. In 2 cases each, the pain was located in the abdomen as follows: generalized; in the right

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8. Babcock, W. W., cited by Fiske.<sup>9</sup>

9. Fiske, F. A.: Intra-Abdominal Torsion of Appendices Epiploicae, with Report of Two Cases and Review of Literature, *Am. J. M. Sc.* **192**:354-360 (Sept.) 1936.

10. Pines, B.; Rabinowitch, J., and Beller, S. B.: Primary Torsion and Infarction of the Appendices Epiploicae, *Arch. Surg.* **42**:775-787 (April) 1941.

TABLE 1.—*Additional Cases of Symptomatic Epiploic Appendages from the Literature*

Author	Patient		Abdominal Pain		Nausea and Vomiting	Tenderness and Rigidity	Palpable Tumor	Leukocytes	Preoperative Diagnosis	Site of Lesion	Comment
	Age	Sex	Location	Duration							
Campbell, H. E.: Chinese M. J. 51: 357-360, 1937	46	M	Left lower quadrant	2 days	Absent	Present	No	13,000	Strangulated hernia	Sigmoid	Mass of fatty tissue, 5 by 3 cm.
Phulachs, P.: Ann. d'anat. path. 15: 297-299, 1938	18	F	Right lower quadrant	2 days	Present	Present	No	.....	Acute appendicitis	Cecum	Normal appendix
Micheli, P. L.: Arch. Ital. di chir. 53: 80-87, 1938	25	F	Left lower quadrant	12 days	Absent	Present	No	.....	Abdominal colic	Sigmoid	Gradual onset of generalized pain, finally localizing
Davis, B. F.: Minnesota Med. 22: 151-153, 1939	35	M	Left lower quadrant	Few hours	Present	Present	No	18,630	Acute diverticulitis	Sigmoid	Torsion of the pedicle; intense passive congestion
Eliaeson, E. L., and Johnson, J.: Surgery 6: 68-73, 1939	47	F	Right upper quadrant	7 days	Absent	Present	No	12,300	Acute cholecystitis	.....	Inflamed epiploic appendage
	38	M	Left lower quadrant	4 days	Absent	Present	Yes	.....	Acute epiploitis	.....	Pain and tenderness well localized
	40	M	Left lower quadrant	3 days	Present	Present	Yes	.....	Diverticulitis	..	Inflamed epiploic appendage
Porter, A.: Bull. et mém. Soc. d'électro-radiol. méd. de France 27: 184-188, 1939	57	M	Generalized	3 mo.	Nausea and constipation	Tenderness	....	.....	.....	Cecum	Periodic attacks of sharp generalized abdominal pain
Walker, H. C.: Am. J. Obst. & Gynec. 37: 811-818, 1939	32	F	Left lower quadrant	3 days	Nausea only	Soreness	Yes	13,800	Twisted ovarian cyst	.....	Pain aggravated by movement; 7 months' pregnancy; tender soft mass along the inguinal region

upper quadrant; in the lower portion of the abdomen. In 1 case, the pain was in the rectum. Nausea and vomiting were present in 12 cases, and nausea alone was present in 6. Tenderness and rigidity at the site of the lesion were found in 21 cases, and tenderness alone was found in 14. A mass was palpated in 7 instances. Fever was present in 1 case and leukocytosis in 2.

A preoperative diagnosis of appendicitis was made in 18 instances and no diagnosis in 8. Diverticulitis was the diagnosis in 5 cases, torsion of an ovarian cyst in 4 and appendicitis and cholecystitis in 2. In 1 case each, the following preoperative diagnoses were made: acute cholecystitis, abdominal colic, ovarian disease, intestinal obstruction, intestinal paralysis, Meckel's diverticulum, sigmoiditis with perforation, strangulated hernia, abscess of the abdominal wall, tumor of the sigmoid, acute epiploitis and torsion of an epiploic appendage.

Torsion of the epiploic appendages was the only lesion found and was responsible for abdominal symptoms in 41 cases; infarcted epiploic appendages and inflamed epiploic appendages were found in 4 cases each.

Of the cases reviewed by Hunt, postoperative death occurred in 2 cases; in those reviewed by Fiske 1 death occurred.

#### CASES ENCOUNTERED AT THE MAYO CLINIC

Since the report of Hunt in 1919, abnormalities of epiploic appendages have been noted at the Mayo Clinic in 178 cases encountered from 1919 to April 1941. Although this number is large, it is not presumed that this is the total number of cases in which diseased tags were present since not all incidental or free tags are found on exploration or are reported when observed. In 18 instances, the tags were intrahernial, leaving 160 cases in which the pathologic processes were intra-abdominal. In 53 of these, the tags were free in the peritoneal cavity. In 1 of the 18 cases, the intrahernial tag also was unattached. In the cases in which the tags were intra-abdominal, 61 tags were considered to reveal evidence of primary involvement of the epiploic appendage, excluding the unattached tags, while in 46, the intra-abdominal tags were considered definitely or probably secondary to other pathologic processes of the abdomen. These related conditions included appendicitis, inflammation of Meckel's diverticulum, pelvic inflammation and tumor, endometriosis, cholecystic disease, peptic ulcer and carcinoma of the large bowel.

The circumstances under which abnormal tags were found incidental to operation for other conditions cover a wide range. Tags were found at operation for conditions in the upper portion of the abdomen in 29 cases and in 120 cases in which operation was performed on the lower portion of the abdomen. In 7 of these 120 cases, operation was performed by the vaginal route.

The pathologic conditions exhibited by the tags reviewed are listed in order of frequency as follows: necrosis, degeneration or gangrene, recorded in 65 cases; calcification, in 39; inflammation, in 31; torsion, in 18; hemorrhagic infiltration, in 14; hyperplasia, in 3; cystic change, in 2; hyalinization, in 1; carcinomatous implantation, in 1. In some instances more than one pathologic condition was present in the same tag. It should be noted that torsion was proved in only 18 cases—in 15 as an incidental finding and in 3 cases in the symptomatic group.

*Symptomatic Conditions.*—We are primarily concerned, from the clinical standpoint, with those cases in which definite symptoms were present. In the present series, there were 10 cases in which diseased epiploic appendages produced symptoms necessitating operative intervention (table 2). In the cases of hernial appendages and in the cases in which the tags were free, instances of definite symptoms could not be substantiated.

Of the cases in which symptoms were present, in 5, appendicitis was simulated and in 1 case each, appendicitis or cholecystitis, pelvic inflammation, carcinoma of the sigmoid, malignant disease in the upper portion of the abdomen and intestinal obstruction. The symptoms presented were reviewed in an effort to determine any factor or factors aiding in the diagnosis of diseased epiploic appendages. Ages of the patients ranged from 19 to 69 years. The ratio of men to women was 6:4. Symptoms were acute or subacute in 4 cases and chronic in 6. The most consistent complaint was pain, which was present in all but the 1 case of chronic obstruction. The pain tended to be mild and constant in 5 cases, but in 4 it was severe and recurrent. Contrary to what is found with typical appendicitis, there was rarely a primary epigastric component with secondary extension and localization of pain. Although nausea and vomiting are considered unusual, they were present in 2 cases in which obstruction was absent.

On examination, localized abdominal tenderness was the chief finding in 7 cases of this series, being acute in only 2. Rebound tenderness was noted in 2 cases and increased muscle tone in 1. In 4 instances, a mass was found in the abdomen or in the pelvis. Rectal examination was of little value, although in 1 case it revealed pelvic appendicitis. The temperature was slightly elevated from 99 to 99.4 F. in 3 cases. In only 2 cases did a leukocyte count of more than 10,000 per cubic millimeter of blood tend to indicate the presence of an inflammatory process.

At operation, the typical finding, instead of the preoperatively diagnosed conditions, was a swollen blue-black or hemorrhagic epiploic tag, generally attached in the sigmoid or the cecal region, which on removal disclosed various degrees of degeneration, gangrene, inflammation or hemorrhage. Torsion was proved in only 3 cases in which symptoms

TABLE 2.—Cases of Symptomatic Epiploic Appendages Encountered at the Mayo Clinic \*

Age and Sex of Patient	Preoperative Diagnosis	Symptoms			Examination					Leukocyte Count	Operative Findings		
		Duration	Pain		Nausea or Vomiting	Elimination	Tenderness	Rebound	Rigidity			Mass	Temperature
			Type	Location									
31 M	Appendicitis	Acute, 2 days	Mild, persistent	Right lower quadrant at onset	None	.....	Grade 1, right lower quadrant	+	0	0	Normal	5,500	Blue-black strangulated tag of the cecum in the right lower quadrant
30 M	Appendicitis	Subacute, 10 days	Sudden, sharp, recurrent	Right lower quadrant	Slight nausea	.....	Grade 3, right upper quadrant	0	Grade 1	0	Normal	10,700	Strangulated epiploic tag in the gastrocolic region
30 F	Appendicitis	Subacute, 8 days	Sharp, shooting, recurrent	Right lower quadrant	None	Diarrhea	Grade 2, right lower quadrant	Marked +	0	0	99 F.	6,700	Necrotic appendage removed from the cecal region
32 M	Appendicitis or cholecystitis	Chronic, 2 months	Moderate, severe, recurrent	Right upper quadrant	None	.....	Grade 2, right upper quadrant	0	0	0	Normal	9,500	Large hemorrhagic epiploic tag with twisted pedicle near round ligament of the liver
35 F	Pelvic inflammation	Chronic, 1½ years	Dull, constant	Pelvis and back	None	.....	0	0	0	Pelvic	Normal	.....	Inflamed epiploic appendage of the sigmoid forming a mass behind the uterus
39 M	Sigmoid tumor	Chronic, 6 weeks	Soreness	Lower part of abdomen	None	Costive	0	0	0	Pelvic	Normal	.....	Adhesions about inflamed tag of the sigmoid, partly obstructing the large bowel
54 M	Abdominal malignant disease	Chronic, 5 months	Acute, recurrent	Right lower and upper quadrants	Present	.....	Grade 1, right lower quadrant	0	0	Right upper quadrant	Slight elevation	9,900	Inflammatory appendage forming a mass near the hepatic flexure
19 F	Appendicitis	Subacute, 5 days	Steady	Above umbilicus	Repeated vomiting	Marked constipation	Grade 1, below umbilicus	0	0	0	Normal	22,000	Inflamed epiploic appendage of the cecum attached to the ileum giving partial intestinal obstruction. Secondary to subacute appendicitis
57 F	Appendicitis	Chronic, 10 years	Dull, soreness	Right lower quadrant	None	.....	Grade 1, right lower quadrant	0	0	Dome-like, right lower quadrant	99.4 F.	4,300	Acutely inflamed epiploic tag of the cecum overlying the appendix. Secondary to chronic appendicitis
38 M	Intestinal obstruction	Chronic, 2 years	None	.....	Present	Costive	0	0	0	0	0	0	Epiploic appendage forming obstructing band attached to the small bowel. Secondary to Meckel's diverticulum

\* In addition to those reported by Hunt <sup>6</sup> in 1919.

were present. Possibly, it had been present in 4 other cases, but this is merely an assumption. In 3 cases of the symptomatic conditions in which primary pathologic processes of the tags were present, masses in the pelvis or the abdomen were palpated preoperatively, suggesting pelvic inflammatory disease, tumor of the sigmoid or malignant disease in the upper portion of the abdomen. These masses proved to be inflammatory masses surrounding diseased epiploic tags of the sigmoid or the hepatic flexure; other pathologic conditions were absent. In 1 case, adhesions produced partial obstruction of the large bowel.

In 3 cases of the symptomatic group, the diseased appendages were associated with other pathologic processes, which probably were primary; the involved tag, however, was the definite contributing factor leading to exploration. In 1 case, Meckel's diverticulum and an epiploic tag formed a ring obstructing the small bowel; in another, an inflamed tag had become attached to the ileum, producing obstruction in a case in which subacute appendicitis also was present. In the third case, exploration was performed because of a domelike mass present in the right lower quadrant of the abdomen. This mass was attributable to inflammation of an epiploic tag with surrounding adhesions. The tag was overlying a chronic catarrhal appendix. In each instance, the patient's condition was relieved or improved by removal of the offending tag.

The weight of patients who had diseased tags was noted, as a definite impression had been obtained that obesity or excessive loss of weight was a factor in the genesis of diseased tags. Considering 150 pounds (68 Kg.) as an arbitrary borderline, it was found that the ratio of obese patients to patients of normal or less than normal weight was nearly 2:1. Among patients who had primary symptomatic tags, the ratio was 5:2, and among those patients who had tags free in the abdomen, the ratio was 15:7.

The following report of a case illustrates the surgical problem presented by acute involvement of an epiploic appendage.

#### REPORT OF A CASE

The patient, a man 31 years of age, registered at the Mayo Clinic on Jan. 26, 1941, and was immediately hospitalized because of mild persistent pain in the right lower quadrant of the abdomen during the previous forty-eight hours. He had been in recent good health except for recurrent bouts of mild pain in the right lower quadrant of the abdomen, occasionally noted in the year prior to registration. At times he had had mild distress in the epigastrium and the right upper quadrant. The attack forcing his hospitalization was more severe than those experienced previously. Nausea, vomiting or other symptoms were not present. On examination, the patient was found to be slightly obese. There was definite intra-abdominal tenderness at McBurney's point, which became progressively more

marked. Rebound tenderness was referred to this region. There was no true rigidity of the abdominal wall. Rectal examination suggested more tenderness high on the right side. Although the temperature was normal and leukocytes numbered 5,500 per cubic millimeter of blood, with 64 per cent polymorphonuclear leukocytes, a diagnosis of appendicitis was made.

Exploration was carried out through a muscle-splitting incision in the right lower quadrant of the abdomen. A bluish black hemorrhagic epiploic appendage with complete torsion of the pedicle at its attachment to the cecum was removed, together with an adjacent inflamed tag. The appendix was normal but was removed (figure). Otherwise the abdomen was normal. The tag measured 1 by 3 by 4 cm. Pathologic section revealed hemorrhagic infarction and fat necrosis. Convalescence was uneventful.



Appendix and epiploic appendages removed at operation.

#### COMMENT

It is evident that pathologic epiploic appendages are observed with sufficient frequency to demand more widespread appreciation of their significance. It is further suggested that the 178 cases reviewed in this presentation probably represent only a portion of the total number of cases which would be revealed by more complete exploration. Although it is difficult to exclude disease of adjacent structures in the causation of 46 of these cases, it is clear that this secondary involvement may progress as an inflammatory or obstructing process requiring surgical intervention. Fifty-four of the tags recorded were detached. It is reasonable to assume that at times these may have caused previous



undiagnosed abdominal complaints. The recognition of these tags is essential. Although tags caused symptoms in only 10 cases in our series, they occur sufficiently often to deserve recognition as a definite cause of intra-abdominal conditions requiring operation.

Unfortunately, no clearcut factors can determine the diagnosis preoperatively, and any diagnosis before operation must be only tentative. A review of the symptoms presented reveals that pathologic conditions of epiploic appendages can suggest practically any acute or chronic intra-abdominal condition from pelvic disease to cholecystitis. The typical picture following acute torsion is considered to consist of moderate localized pain and tenderness in the abdomen of a rather obese young patient. There is little generalized reaction; the epigastric component of appendicitis and identifying criteria of other pathologic processes are absent. Actually, however, the temperature may be elevated and the number of leukocytes increased. Nausea and vomiting do not exclude the diagnosis, and abdominal masses or signs of obstruction may be encountered. It is apparent, therefore, that generally the diagnosis can be suggested only by the absence of other localizing signs.

Nevertheless, disease of the tags can be of definite importance to the patient. Although simple necrosis of the pedicle may allow a tag to detach and not cause further trouble, the presence of infection in the diseased epiploic tag by organisms derived either from contiguous bowel or some other structure may lead to peritonitis or localized reaction sufficient to cause obstructing lesions. That this outcome is sufficiently frequent to be a real hazard to the patient is revealed by a review of our cases in which symptoms were present and suggests the need of immediate operative treatment whenever diseased tags are encountered.

#### SUMMARY

An analysis of 178 cases in which abnormal epiploic appendages were encountered at operation at the Mayo Clinic from 1919 to April 1941 is presented. Of these cases, 61 represent instances of true intra-abdominal primary pathologic processes of the attached tag. The literature is reviewed, summarizing the cases of true symptomatic involvement of diseased epiploic appendages. Forty-nine were found to the date of writing. To this group we added 10 cases. Consideration is given to the symptoms and signs presented by diseased epiploic appendages in an effort to aid in diagnosis. Although a typical picture may be described, it is rarely adhered to, and even when the picture is present, the suggested diagnosis must remain tentative. The various conditions simulated and the pathologic states encountered at operation are discussed, and the surgical significance of epiploic appendages as a cause of acute and chronic abdominal conditions is stressed.

# ACUTE SURGICAL PAROTIDITIS

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Under the title "acute surgical parotiditis" may be grouped all acute inflammations of the parotid gland except that occurring in mumps.

The condition has been written about under many other names. It should not be called secondary parotiditis, for it occurs also as a primary disease. The names "septic," "gangrenous," "suppurative," "phlegmonous" or "necrotic" describe only various phases of the one disease—differences in degree of inflammation. "Postoperative" is no more appropriate than "postpneumonic," since the disease occurs after a great number of other conditions—Custer enumerated some twenty-five, and the same disease occurs in those otherwise healthy (Nicol). It has been called sympathetic parotiditis because it was known to occur after injuries to the testicle and sometimes after even slight operations on the genito-urinary tract, e. g., passing of a sound, placing of a pessary or catheterization of the bladder (Paget). Later, when surgeons began to operate in the abdomen, it was thought to follow especially operations on the ovaries and the uterus. Möricke, remembering the metastasis of mumps, reasoned that if an inflammation of the parotids could excite an inflammation of the ovary, the converse also must be true. Bumm thought it an ascending infection but concluded that Möricke was right—"the parotid had its vascularity increased by operation on the ovary." There were many who agreed with Möricke, e. g., Paget and Goodell, but the theory seems to have been abandoned.

The condition is more often referred to in the literature as "parotitis," but the word "parotiditis" indicates that it is an inflammation of the parotid. We are then here concerned with an acute noncontagious, non-specific inflammation of the parotid gland which arises from a variety of causes and which is, no matter what the cause, best treated by surgical means—hence the name.

It was Hippocrates who first described parotiditis, but not surgical parotiditis, for he clearly told of how it occurs in epidemic form and

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\* Dr. Coughlin died on May 22, 1940. This paper was begun as a joint study and was completed by the junior author.

sometimes causes testicular inflammation. Surgical parotiditis never does either of these things. Celsus, however, spoke of a variety of parotiditis following protracted fevers and advised that the involved parotid be opened as soon as possible, while Galen spoke "of parotiditis that is of abscesses near [juxta] the ears" and advised poulticing. Murat<sup>1</sup> stated that the disease was known to Avicenna and that according to him, those of slow development were opened with the cautery and the others poulticed or opened with a knife. Avicenna, we have not been able to consult! Paré recognized this form of treatment. Petit (who died in 1750) discussed the subject and advised early opening no matter how hard. In the works of Sydenham, Cullen, Fothergill, Cheselden, Hunter and Astley Cooper we found no reference to it, but in Good's book, published in 1829, it is described, and the author criticized Cullen for having placed it "among the warts and skin lesions." Good plainly referred to the two varieties, but he somewhat confused the phlegmons with the new growths. Rust, in Germany, recognized both varieties and advised poulticing the surgical kind and not opening too early. Benjamin Brodie, in England, had about the same idea at that time. Cruveilhier, in France, who, like Hunter in England, did much to interest the world in the study of pathology, gave a description of this condition to which little, if anything, of importance has ever been added. He described and illustrated the condition, was of the opinion that the inflammation ascends from the mouth, that suppression of the saliva precedes it and that gangrene and suppuration are often present together.

It is strange how many articles give credit for all this to Virchow, who, writing twenty years after the publication by Cruveilhier, himself gave first credit to Cruveilhier for having had the correct idea of the pathologic nature of the condition. These conclusions of the celebrated French pathologist were confirmed first by Virchow and then by Hanau and others. Mosler, acting on the assumption that their ideas were correct, studied the saliva and concluded that its reaction changed in fever. He thought that he prevented the complication in typhoid by catheterization of the ducts and advised this as prophylaxis.

Galippe proved that even in young infants there are bacteria in the ducts although the glands are healthy. Girode, making bacteriologic and histologic studies of glands and ducts, found that the evidence in 12 cases pointed toward an invasion from the mouth. The bacteria in the ducts were fewer while the animal ate. Gilbert and Lippmann confirmed this in 1904. Claisse and Dupré in 1894 removed a normal gland as well as

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1. Murat's article is found in a large encyclopedia arranged by the best authorities in Paris about the beginning of the last century, and there may be found almost everything that was then known on almost any subject in medicine or surgery.

the diseased one post mortem and studied both. They found the same bacteria in both and pus in both, although there was no fluctuation in either. There were some areas in each gland that presented the same histologic picture, but catarrh of ducts with intracanalicular debris, even in those parts least inflamed, pointed to an ascending infection. Claisse and Dupré came to conclusions, it would seem, before they made their animal experiments. They were able to produce parotiditis in the animal if they first injured or obstructed a gland or a duct—but not always. We found no record of experimental attempts made by them to produce parotiditis by blood stream infection. Rost, however, in 1914, tried to induce parotiditis not only through the blood stream and through the duct but also by contiguity. In both of the first two methods, he was successful; in the last, he was not. He had his best success in exciting parotiditis by blood-borne infections. By microscopic examination, he was unable to distinguish the blood stream variety from that arising from duct infection. Berndt, Buck and Buxton in 1931 repeated such experimental work. They found it easier to excite parotiditis by duct injection than by injections through the artery. They also found a difference in the histologic picture. The route of infection, therefore, is not proved. Yet it seems that most of those who have written about it were of the opinion that it is an ascending infection. However, there have been many apparently contradictory phenomena, and all have not accepted that theory. Many have expressed the opinion that the infection is carried to the gland by the blood. In 1880, Wendt studied a gland twelve hours after the onset of the disease and concluded that the ductal changes were secondary. Since then the doubt has existed. Those who contend for an ascending infection base their belief on the microscopic picture as interpreted by Virchow and others, and maintain that were the condition metastatic, one would always find the organism present in an original focus, that there would always be a suppurating wound or focus to precede the parotiditis and that other metastatic abscesses would always accompany, precede or follow. Others reply that were it an ascending infection, there should be found the same organisms that are present in the mouth and never a sterile culture from the gland, that mouth infections would favor it, whereas it is an unusual complication of any acute mouth or throat infection and that if it is an ascending infection, it must be explained why the submaxillary gland does not become inflamed more often, since the papilla is more likely to admit a foreign body and stones are more common in Wharton's duct than in that of Steno.

Seifert claimed that the mucin content of the submaxillary gland hindered bacterial growth. He found that the less the saliva, the more the bacteria and that in and near the canine fossa, bacteria were more

numerous than under the tongue. We have not found confirmation of his experiments.

Rolleston and Oliver, in 1909, reviewed the occurrence of parotiditis in 1,000 cases of peptic ulcer treated medically. They found that parotiditis occurred ten times more frequently in cases of peptic ulcer treated by oral starvation (470 cases with 4 per cent parotiditis) than in cases in which the patient was allowed water by mouth (530 cases with 0.4 per cent parotiditis). This is a most valuable observation. Cope, in Mesopotamia in 1919, had 9 cases of parotiditis, all in the hottest weather (120 F.) and all in dehydrated and debilitated patients.

#### ANATOMY OF THE PAROTID GLAND

The parotid gland is the largest of the salivary glands and secretes a watery saliva. The gland is a compound acinar gland of the racemose type which arises in the embryo as an outgrowth from the alveololabial sulcus and passes outward and backward as a process of giving rise to buds, which divide to form the lobules of the gland. The epithelium of the terminal ends forms the secretory alveolar epithelium and that of the stalk gives rise to the lining epithelium of the ducts. The parotid duct (Steno's or Stensen's) is similar to, but not as large as, the ureter and empties by peristaltic waves.

The main portion of the gland is superficial and somewhat flattened and quadrilateral in shape; it lies anterior to the ear and below the zygoma with one extension below the ear, backward and upward behind it toward the base of the mastoid and another passing medially behind the ramus of the mandible to the side wall of the pharynx, the glenoid portion of this extending toward the tympanic region. This glenoid portion of the gland comes into direct relation with the cartilaginous part of the external auditory canal. There are several vertical fissures (Santorini) in that cartilage in this region, covered only by a fibrous tissue. Much has been made of this as a pathway for lymph flow between middle ear or mastoid and parotid. However, "the fissures are in the posterior superior wall in the inner end of the cartilage of the canal" (Gray).

The parotid duct leaves the anterior portion of the gland about a fingerbreadth below the zygoma, passes over the anterior border of the masseter muscle and into the mouth through the buccinator muscle to end in the papilla opposite the second upper molar tooth. Sometimes the accessory glandule, the socia parotidis, lies along its upper border and from this a small duct joins that of Stensen before the latter leaves the masseter muscle.

The facial nerve emerges from the skull between the mastoid and styloid processes and finds its anterior and external aspects in immediate

relation with the parotid gland. The nerve gives off the posterior auricular branch and branches to the digastric and stylohyoid muscles and then enters the parotid gland; altogether, its course from skull to gland is usually not more than 1 cm.—often not that long. As soon as it enters the gland, it breaks into branches which unite with one another and again divide, reunite and subdivide irregularly to form the plexus parotideus or pes anserinus in the deep half of the gland. The three divisions of the nerve leave this plexus and course toward their final destinations, emerging from the gland near or quite at its anterior border. This arrangement of the nerve is important to remember when operating on the gland. It will be remembered that this nerve travels through the tympanum covered only by the mucous membrane and along its perineural lymph space infection might easily travel from middle ear to parotid.

The parotid gland is in close relation with the upper half or two thirds of the external carotid artery. The gland with facial nerve and temporo-maxillary vein in its substance lies external to the artery below, but as the artery ascends, it enters the gland. At the level of the neck of the condyloid process, the carotid ends by dividing into the internal maxillary and superficial temporal arteries. This is just about the level of the external auditory meatus. The superficial temporal ascends through the gland, gradually becoming more superficial and leaves the gland entirely by crossing the zygoma just in front of the ear. While in the gland, it gives off the transverse facial which runs forward in the gland below the zygoma and above Stensen's duct. The internal maxillary runs forward to disappear under the neck of the mandible.

The veins accompanying the arteries lie on their outer sides and hence are more superficial and have a longer course within the gland substance than the corresponding artery. Most important and largest is the temporomaxillary vein formed in the gland just in front of the meatus externus by the union of the temporal and internal maxillary veins. It courses downward and soon divides—an unusual thing for a vein to do. Its anterior branch courses forward to become superficial and join the facial vein just deep to and below the lower border of the jaw and about a fingerbreadth in front of its angle to form the common facial; the posterior branch, descending, joins the posterior auricular within the gland to form the external jugular behind the angle of the jaw.

It will thus be obvious that to cut freely into the gland would probably cause profuse bleeding and perhaps divide at least some of the branches of the seventh cranial nerve. It is also to be noted that the least vascular part lies close to the ear. Incisions here would be less likely to have unpleasant consequences.

Enclosed as it is in a fascial sheath, the parotid gland is actually surrounded by a lymph space. It should not be forgotten that each vessel that enters, leaves or lies alongside of the gland, is surrounded also by its own sheath, again a lymph space, and that on its deep aspect, between the gland and the pharyngeal wall, lies a layer of loose cellular tissue in which lie the great vessels and nerves and a rich venous plexus; again such loose, cellular tissue becomes an enormous lymphatic reservoir. In addition to this, however, the gland has a system of lymph glands and vessels of its own. The glands are two or three in number, lie in front of the tragus and usually at least one is outside the sheath. There is said to exist a direct lymphatic connection between the middle ear, the deep portion of the auditory canal and the parotid through the previously mentioned slits in the anterior wall of the canal. The efferent drainage is to both the superficial and the deep cervical glands, and usually those under the sternomastoid just below the gland show the greatest swelling in infectious parotiditis.

The fascia covering the gland is derived from the cervical fascia. It consists of: (1) an external layer attached to the zygoma above, to the external auditory canal near its outer end, continued down as the cervical fascia below and blended with the fascia covering the masseter anteriorly; (2) an internal layer lining the parotid recess, attached to the periosteum and perichondrium over the external auditory canal and glenoid fossa posteriorly, to the styloid medially, to the stylomandibular ligament and to the deep cervical fascia below. Together the two layers form a tough and unyielding capsule with its weakest points where the layers join the cervical fascia below and in the region of the auditory canal. This fascia is closely applied to the gland and adheres firmly to it by means of fascial septums which pass from its deep surface inward between the lobes and lobules so that the fascial capsule cannot easily be reflected nor can the capsule yield easily to accommodate the exudate when acute inflammation occurs in the gland. The high tension soon cuts off the circulation, and this is the chief reason why gangrene of the gland occurs so early in acute infections of the parotid.

#### PATHOLOGIC CHARACTERISTICS

There are four possible routes by means of which infection may gain entrance to the gland: (1) through the lymphatics; (2) through the blood stream (hematogenous); (3) via the parotid duct, and (4) by direct extension from contiguous tissues.

Although there is said to be no direct lymphatic connection of the parotid with the oropharynx and although it has been said not to follow conditions affecting the mouth and the throat, we noted the condition after sore throat and after tonsillectomy as well as after tooth extraction

(cases 19, 28, 29 and 30). Of course, this does not prove direct lymphatic extension, but there is that possibility. We have noted before that lymph from the middle ear and the tympanum drains into the parotid lymph nodes. When the middle ear is infected, direct extension along the lymphatics can lead to abscess in and around the anterior auricular node or to general parotiditis (case 25), and various authors, e. g., Hempstead, Adams and Wilson, reported cases of parotiditis associated with otitis media resulting, in their opinion, from direct lymphatic extension to the parotid. In some cases, the resulting inflammation of the parotid is diffuse and in others an abscess in the region of the superficial lymph nodes. A case was reported as following an infected wound of the forehead (Blair). Our case 34 followed a blow of a fist. However, we find no experimental or clinical proof of the extension of the infection to the parotid by way of the lymph channels.

We have referred to the experimental work in which it was shown that parotiditis may be produced by blood stream infection. Cases of parotiditis with identical bacteremia or septicemia are not frequent in the literature, and none were present in our series. However, a case from the private practice of one of us (W. T. C.) will be cited later to show that such may happen.

The arteriolar and capillary bed in the gland does not conform with the terminal type, and although lodgment of bacteria in the gland during septicemia is possible, in the literature parotiditis has seldom been reported as associated with pyemia or septicemia—a blood stream infection accompanied by parotiditis is not often found. In Paget's 101 cases, there were only 7 in which other lesions pointed to pyemia.

We have mentioned the arguments pro and con infection via the duct. In our opinion this is by far the most common way. The reports of Rolleston and Oliver are convincing. Our own experience forces us to believe that a dry mouth is almost always present—for one reason or another the saliva does not flow. Bacteria are always to be found within the orifice of the duct (Galippe, Girode, Claisse and Dupré). Because they are not constantly washed out, they ascend. The lowered vitality shown to be necessary by all experimental work furnishes the opportunity for their further growth.

We do not find that parotiditis has been experimentally produced by infecting the contiguous tissues, and although cases have been recorded as following trauma to tissues near by, there may often be some doubt as to the correctness of the diagnosis of parotiditis. Claisse and Dupré, by injuring simultaneously both gland and duct by trauma, excited parotiditis.

Between 1836 and 1842, Cruveilhier published and illustrated a description of this disease. He contended that the infection ascends



from the mouth and finally reaches the terminal canaliculi and acini and then invades the cellular tissues. In 1858, Virchow in his usual way, went thoroughly into the question and concluded that "Cruveilhier was right—it ascends the duct and invades the gland substance as broncho-pneumonia invades the lung." In 1880, Wendt examined a gland which had become inflamed only twelve hours before the patient died. He thought that the disease was brought to the gland by the blood and that ducts and acini were secondarily involved. Studies were made also by Cornil and Ranvier.

Hanau, after studying the glands in 4 cases microscopically from the pathologic point of view, agreed with the first authors. Since then much has been written on both sides of the question. We think the studies of Custer and co-workers are the best that have been made in recent years and have the best verified bibliography. They are supporters of the ascending infection theory.

Practically all are in agreement with regard to the pathologic histologic nature. There are pus cells in ducts, acini and interacinous tissue. The earliest stages are about the canaliculi, in which exists mild catarrh with simple accumulation of desquamating epithelium. There is pericanalicular accumulation of round cells. The capillaries and the smaller vessels contain blood clot. According to Claisse and Dupré and others, the changes are least marked toward the periphery of the lobules, and often whole lobules escape. These are changes agreed on by the French and most other authors. Some, e. g., Berndt, go so far as to say that the larger ducts are involved in ascending infections, the smaller, in those deriving from the blood stream. At first, myriads of small aggregations of leukocytes form in canaliculi and distending these, rupture their walls and result in minute abscesses.

The exudation ensuing on account of the inflammation cannot easily find a place for itself because of the dense connective tissue capsule and the almost equally strong interlobar and interlobular septums extending in from the deep surface of this capsule. As the tension rises, first the venous circulation is retarded, and if the process progresses, it need not be long until complete stasis occurs. It also is probable that in certain infections the toxins liberated are of such a nature as to destroy chemically cells with which they come into contact. However it may be, any lobule or lobe or any number of them or even the whole gland may be so deprived of its circulation that gangrene may supervene in an extremely short time. Because of the same strong septums and dense connective tissue capsule, accumulation of pus is hindered, and pus is prevented from appearing in the fatty layer between gland and skin, so that although pus is present in abundance, the clinical sign of its presence—fluctuation—can never appear until late in the disease (Wag-

ner, Picqué, Petit and others). We have found early gangrene and early general purulent infiltration, but never have we found early gross abscess formation.

It has been stated before that the capsule is less dense and firm on the deeper surface of the gland. Should a deep portion of the gland become first involved, early extension through this part of the capsule is probable. There is an extremely weak spot below and anterior to the styloid process and along the stylohyoid muscle. Thus the precincts of the submaxillary space may become invaded, and the diagnosis of inflammation of the submaxillary gland may be wrongly made. From here it is easy for the pus to travel downward along the great vessels, or breaking the posterior part of the capsule deep to the anterior margin of the sternomastoid, it spreads directly downward and backward under this muscle and under the trapezius. Mastoiditis has accompanied it; whether as a cause or a consequence is not certain (Picqué). Another weak spot in the wall of its lodge is in the anterior wall of the external auditory canal, and through this, pus may break before suppuration is thought to exist. Indeed, it has even broken into the ear after operation because the gland capsule was not incised. Again from the deep aspect higher up, pus soon comes to lie directly in contact with the base of the skull and even extradural abscess, meningitis and psychic phenomena have been caused by intracranial spread (Everke, Picqué). The temporomandibular joint may become involved, and permanent constriction of the jaws may result. This constriction is always present early, the jaws being reflexly closed because any attempt to open compresses the inflamed gland. Some stiffness may remain, and one of us (W. T. C.) has reconstructed a temporomandibular joint in which bony ankylosis was said to have followed parotid inflammation.

The papilla is sometimes swollen, and the mucosa about it reddened, but not in all cases. Sometimes pus is seen exuding from the papilla. From ducts of the acutely inflamed glands, we have not been able to express saliva or pus in any appreciable quantity, but from the mildly or subacutely inflamed glands, one of us (E. R. G.) has expressed shreds of mucopus. There is often mention of plugs of pus having been expressed from the duct (Johnson).

We have stated that clots are to be found in many of the smaller blood vessels. It is not unusual to find at operation larger veins so filled with clot that they do not bleed when severed. This we have observed of the external jugular vein and the two veins which form it and also of the superficial temporal vein. Virulent parotiditis might thus quickly send septic emboli to the lungs.

It has been remarked that gangrene is often present. This may be complete in twenty-four hours (cases 16, 26, 39 and 40), and it may

destroy the facial nerve permanently in that time (case 26). Gangrene may be present, and cultures yet fail to show any growth. But sterile cultures from the duct are rare.

#### BACTERIOLOGIC FINDINGS

The most commonly found organism is the staphylococcus, but streptococcus and a rod, gram-positive or gram-negative, are frequent enough. It is not unusual to find one or more organisms in the duct and others different in the gland. Not more than once have we seen the organisms of Vincent, although we have several times expected to from the odor.

We were able to have cultures from 37 incised glands, but in only 10 of these had cultures been made also from the ducts.

*Cultures from the Duct and the Incised Gland.*—Cultures were made from the ducts and the incised glands of 10 patients. The growths obtained were as follows:

Staphylococcus alone in both the duct and the gland (aureus, or aureus and albus).....	3 cases
Staphylococcus in the duct; staphylococcus and gram-positive rods in the gland.....	1 case
Staphylococcus and streptococcus in the duct; staphylococcus alone in the gland.....	1 case
Gram-positive rods and staphylococci in the duct; staphylococcus in the gland.....	1 case
Gram-positive rods and staphylococci in the duct; no growth from the gland.....	2 cases
Gram-positive bacilli from the duct; no growth from the gland..	1 case
Gram-positive bacilli and spirilla from the duct; no growth from the gland.....	1 case

*Cultures from the Incised Gland.*—Twenty-seven cultures from the glands (cultures from the duct forgotten) yielded growths of the following organisms:

Staphylococci from 23 glands, with 7 deaths
Staphylococci and gram-negative rods from 1 gland; no death
Paired gram-positive cocci (pneumococci?) from 1 gland; no death
Hemolytic streptococci from 1 gland; no death
Nonhemolytic streptococci from 1 gland; no death

The predominance of staphylococcus accords with the general experience. We were able to have blood cultures from 17 patients, in most cases daily. In only 1 case (55) did the blood stream show infection (*Streptococcus haemolyticus*), but the gland gave a pure culture of staphylococcus. In 10 cases (6, 16, 19, 26, 30, 39, 40, 45, 46 and 51), the

gland was incised within twenty-four hours, and in only 3 of these (6, 19 and 26) was pus visible, although in all there was acute inflammation. In 5 of those in which pus was not demonstrated, cultures were made, and all yielded a growth of staphylococcus. There were 12 cases in which the gland was incised during the second and third twenty-four hours. In 8 of them, no pus was demonstrated, but in 7 of these cultures were made, only 1 of which was negative. In 4 in which there were infected abdominal wounds, both the wound and the gland were cultured. In only 1 (case 36, a wound abscess) were the same organisms present in both the wound and the parotid.

#### INCIDENCE OF PAROTIDITIS

The incidence of surgical parotiditis has received little attention, and the disease is considered infrequent, while it really occurs more often than supposed.

Piqué listed only 2 cases occurring among 7,200 surgical procedures (1:3,600). Beckman recorded 3 cases in 6,825 surgical procedures (1:2,270). Collins reviewed 8 cases in 6,100 cases of postoperative abdominal conditions (1:762). Charlton reported 13 cases in 2,716 surgical procedures (1:209). Combs reported 9 cases among 13,000 cases in which anesthesia was employed (1:1,450). Lynn gave 3 cases in 947 operations (1:315). All these were cases of postoperative parotiditis. Little reference is made in the literature to the occurrence of parotiditis in the medical services.

We have studied the incidence of parotiditis in our hospitals from January 1926 to January 1939. Our hospitals are two in number, namely, St. Mary's Hospital and Firmin Desloge Hospital. (The latter replaced the St. Mary's Infirmary in 1933.) The St. Mary's Hospital is regarded as "the private pavilion" of the University's hospitals, while the Firmin Desloge Hospital, "a hospital for poor people and people of moderate means," is the clinic hospital. The St. Mary's Hospital is an open hospital wherein the faculty of the school of medicine exercises a "power of selection" of the visiting staff, and Firmin Desloge Hospital is open only to members of the teaching faculty. The cases herein reported, then, are not those of any one surgeon and may be said to represent the general surgical practice in St. Louis. During the period of our study, 95,367 patients in all services were admitted to our hospitals, and in these there were altogether 56 cases of parotiditis. However, 12 of these cases did not develop in the hospital, but the patients were admitted because of the condition. Therefore, in 95,355 hospital patients, the disease developed 44 times (1:2,167).

In the medical services alone there developed in the hospital 16 cases in a total of 28,456 patients; 8 patients had the disease when they

came in. Thus, 1 case developed in the medical service for each 1,779 admissions.

In all surgical services, to which 45,389 patients were admitted, there were 32 cases of parotiditis, but 4 of these were present when the patient entered, so that only 28 cases developed in the hospital (1:1,621), and 23 of these followed major operations (1:650).

A striking fact is the complete absence of parotiditis among the 21,514 obstetric and newborn patients.

#### REPORT OF CASES

##### *Twenty-four cases complicating medical conditions*

CASE 1 (St. Mary's Hospital).—A white man aged 60 entered on May 20, 1928, following the onset of lobar pneumonia which involved the entire right lung. The patient was recovering when, on June 3, he complained of a sore neck in the region of the parotids. The gums were described as dirty and bleeding at the time of the onset of parotiditis. By June 5 there was bilateral swelling of the parotids, the right gland being the more swollen. The white blood cell count was 12,400. During the acute swelling, swallowing was difficult. Ice packs were applied and oral hygiene was given. The pain and the tenderness subsided by June 15, the twelfth day of parotiditis, and the white blood cell count dropped to 5,600. The patient recovered.

CASE 2 (St. Mary's Hospital).—A white man aged 23 years entered in diabetic coma on Sept. 7, 1929. The blood sugar content was 666 mg. The pharynx was red and injected and the teeth carious. The following day, when the patient was conscious, he complained of sore throat and pain in the neck. Examination revealed foul breath and ulcerated gums. During the night, swelling of the left parotid began. The white blood cell count was 21,000; the temperature was 102 F. Fluids were given by mouth, and ice packs were applied to the gland. The inflammation and the swelling increased, and within forty-eight hours, the swelling involved the eyelids, the cheek and the neck, extending around the back of the neck. There were purulent discharge from the external auditory meatus and fluctuation in the temporal region. The skin overlying the gland and the neck was red and brawny. With the patient under anesthesia induced with ethylene, a Y incision was made over the left parotid, freeing a large amount of pus. The swelling and inflammation of the gland gradually subsided, and the wound drained freely. The wound was healing, but there was some discharge from the wound when the patient was sent home on September 20.

CASE 3 (St. Mary's Hospital).—A white man aged 53 years entered on Nov. 9, 1929, with the diagnosis of advanced cardiovascular renal disease with hypertension. The blood pressure was 190 systolic and 90 diastolic. The nonprotein nitrogen was 93 to 120 mg. The urine showed albumin, cells and casts. The patient's tongue was coated; the teeth were unclean, and the pharynx was covered with a mucopurulent material. On Nov. 23, 1929, a rapidly developing, diffuse, hard and tender swelling occurred in the right parotid area. There was no redness of the skin, but the area was painful and edematous. The left parotid area was also slightly swollen and tender. The white blood cell count was 7,300. Mouthwash, oral hygiene and ice packs were used. By the third day, the left side had completely subsided. The next day there was an increase in the right-sided swelling; no pus was visible at the duct papilla. The inflammation gradually subsided to December

6, the thirteenth day of parotiditis. The patient was complaining of severe precordial and substernal pain on December 6 and 7 and died suddenly on December 8. Autopsy was not performed.

CASE 4 (St. Mary's Hospital).—A white man aged 25 years entered March 30, 1931, with marked swelling of both parotids. The swelling began in both glands suddenly forty-eight hours before entrance, but the right gland enlarged more rapidly than the left. On entry, examination revealed that both glands were hard, hot and tender with red overlying skin. The patient had difficulty in swallowing. The mouth was foul, there being marked pyorrhea and pharyngitis. Both papillae of the ducts were red and elevated, and pus was draining freely into the mouth. There was swelling of the soft palate and some swelling and tenderness of both submaxillary glands. The temperature was 102 F. The white blood cell count was 14,000. Throat cultures revealed pneumococci and staphylococci. Sodium perborate gargles were used frequently, and hot packs were applied to both glands. Under conservative treatment, the glands gradually subsided, draining into the mouth, and the patient was discharged on April 11.

CASE 5 (St. Mary's Hospital).—A white woman aged 69 years entered in a semiconscious state with a diagnosis of secondary parotiditis and diabetic coma on Sept. 16, 1932. The blood sugar content was 550 mg. The white blood cell count was 15,500. Four days before entry, a swelling began below the left ear. On entry, examination revealed a red firm tender swelling extending from under the left ear and jaw up to the hair line accompanied by edema of the eyelids. Pus was draining from the left external auditory canal. The mouth was dry, and the pharynx was injected. The temperature was 100 to 101 F. The pain in the gland persisted. On September 20, the eighth day, with the patient under local anesthesia, a vertical incision 1 inch (2.5 cm.) long was made in front of the left ear, revealing a gangrenous gland and freeing a small amount of pus which on culture yielded a growth of *Staph. albus*. By September 21, swelling of the right parotid occurred and rapidly increased so that the edema had closed both eyes. Pus was draining from the right auditory canal. After twenty-four hours, ice packs were changed to hot wet packs. On September 23, pus was draining into the mouth "in the region of both tonsillar fossae." By September 25, there was gangrenous discoloration back of the left ear in the mastoid area, but there was rapid decrease in the size of both glands with profuse drainage from the left gland. The patient was discharged on September 28, with the left gland draining and a gangrenous area present behind the left ear at the mastoid tip.

CASE 6 (St. Mary's Hospital).—A white woman aged 21 years entered Oct. 9, 1932, with pernicious vomiting from malignant hypertension with nephritis. The blood pressure was 210 systolic and 140 diastolic. The nonprotein nitrogen was 75 mg. The mouth showed poor hygienic condition, and treatment for this was given. The malignant hypertension was rapidly progressive. Throat culture before onset of parotiditis showed gram-positive cocci in gray colonies. On November 3, the patient's temperature rose from normal to 101 F., and swelling began in both parotids, but chiefly in the right, which was swollen, sore and tender. Ice packs were continuously applied during the first twenty-four hours. The tongue and the mouth were dirty, and cleansing mouthwash was given. Blood cultures during the first forty-eight hours were negative. The swelling of the right gland increased rapidly in twenty-four hours, and respiration became labored. The gland was opened twenty-four hours after onset of the disease, and 10 cc. of pus was freed, which on culture yielded a growth of gram-positive cocci in clusters. Cultures from

the duct orifice grew gram-positive cocci in groups and chains. Within forty-eight hours of the onset of parotiditis, the patient became comatose. The parotid swelling subsided, but the patient's temperature rose to 104 F., and the nonprotein nitrogen above 75 mg. The patient died on November 5 within forty-eight hours of the onset and twenty-four hours after operation. Autopsy was not done.

**CASE 7 (St. Mary's Hospital).**—A white man aged 84 years with the diagnosis of cerebral anemia, aortitis and advanced arteriosclerosis, entered in an irrational state on Jan. 8, 1933. On the second day, a small lump, hard and tender, appeared at the angle of the right jaw. It was diagnosed as parotiditis. The next day the swelling increased rapidly, extending and enlarging below the right mandible. No stone was palpable, and no pus could be expressed from the duct, which was described as normal. The white blood count was 26,500 with an infectious Schilling count. The patient's temperature rose from 99.8 to 103 F. He grew rapidly worse, became weaker and died January 15 on the fifth day of parotiditis. No autopsy was performed.

**CASE 8 (St. Mary's Hospital).**—A white man aged 49 years entered on April 28, 1933, with acute swelling of the left parotid of four days' duration, diagnosed as acute secondary parotiditis. There was acute inflammation and swelling in the left parotid area with red overlying skin. Pus exuded from the orifice of the left duct, and the papilla was red and edematous. The temperature was 102.4 F. The white blood cell count was 19,000 with an infectious picture. The gland was incised by a vertical incision in front of the ear, and hot packs were applied. Culture from the pus found in the gland gave a growth of staphylococci. The gland tissue was edematous with multiple pus pockets. Within forty-eight hours, the swelling had decreased, and the patient was discharged after seventy-two hours with a draining parotid wound, eight days after onset.

**CASE 9 (St. Mary's Hospital).**—A white woman aged 71 years with the diagnosis of bilateral nephrosclerosis, lithiasis, pyelonephrosis and cardiovascular disease, entered July 24, 1934, semicomatose in acidosis. Marked pulmonary edema was present. On July 29, swelling of the left parotid began, and ice was applied. After forty-eight hours, an enlargement of the right parotid occurred, more marked than on the left and more tender and painful. The temperature was 101.8 F. A blood culture was negative. In the next two days, the right gland became less tense, and on the seventh day after onset, with the patient under local anesthesia induced with procaine hydrochloride, the right gland was opened through a 1 inch (2.5 cm.) incision in the capsule. The gland was creamy white with small "nodules of pus." The patient was in a critical condition at all times and died on August 4, six days after onset. Death was attributed to uremia and toxemia.

**CASE 10 (St. Mary's Hospital).**—A white woman aged 49 entered on Sept. 5, 1935, with a history of chronic otitis media on the right and a swelling in the left parotid area present for four days. A similar swelling had occurred in the same gland a year before. On entry, the left gland was swollen, painful and tender but not red. Oral hygiene was good. The white blood cell count was normal. Heat was applied and mouthwash given frequently, and the swelling gradually subsided. The patient was discharged on the eighth day after onset. No stone could be found by roentgen examination.

**CASE 11 (St. Mary's Hospital).**—A white girl aged 9 years with history of bilateral mumps a month before entered on August 25, 1935, with the diagnosis of acute secondary parotiditis. There was moderate swelling of the right parotid,

which increased in size, becoming tender and painful. The white blood cell count was 8,500, and the temperature was 100 F. The buccal membranes were red and injected on the right side. By September 4, ten days after onset, the swelling had restricted opening of the mouth, and with the patient under local anesthesia the gland was incised vertically in front of the ear, freeing about 10 cc. of pus, which on culture yielded a growth of *Staph. albus*. Drainage of the pus continued until the patient was discharged on the sixteenth day.

CASE 12 (St. Mary's Hospital).—A white man aged 25 with a history of rapidly increasing jaundice, nausea and vomiting entered Sept. 29, 1935. The condition was diagnosed as acute catarrhal jaundice. The white blood cell count was 17,600; the temperature was 99.4 F. The mouth and the lips were dry, and the tongue was coated. On October 7, a swelling of the left parotid occurred; it became large, painful and tender. The white blood cell count was 21,000; the temperature was 99 to 100 F. Ice packs were applied and oral hygiene instituted. The swelling decreased in size but was still present when the patient left the hospital on October 8.

CASE 13 (St. Mary's Hospital).—A white woman aged 45 with a diagnosis of coronary and hypertensive vascular disease entered Nov. 4, 1935, after a recent abdominal upset thought to be pancreatitis. The nonprotein nitrogen was 55 mg. On the day of entry, a hard swelling 1 inch (2.5 cm.) in diameter was palpable in the left parotid region. The white blood cell count was 7,225, with a shift to the left. Ice packs were applied and gargles given. In twenty-four hours the upper lobe was enlarged and there was a hard mass in the lower parotid area. In forty-eight hours, the inflammation began to subside, and the patient was discharged on the fourth day after onset. The patient's temperature ranged from 98.6 to 99 F.

CASE 14 (Firmen Desloge Hospital).—An elderly white man aged 87 entered on Sept. 6, 1935, because of urinary obstruction arising from a malignant papilloma in the urinary bladder. There were metastases to the lung confirmed by roentgen examination. The patient had also anginal attacks due to advanced cardiovascular disease. In addition he had severe arthritis and lived in the ward for patients with incurable diseases. In November 1935, he endured severe anginal attacks and rapidly grew weaker. On Jan. 22, 1936, a swelling began suddenly in the left side of the face, rapidly enlarging and becoming hot and tender and red. The patient's temperature rose from 99 to 103 F., and he died suddenly within twelve hours after onset. There was no autopsy.

CASE 15 (St. Mary's Hospital).—A white woman aged 66 years with the diagnosis of advanced cardiovascular disease with hypertension, entered on Dec. 27, 1935, following an episode of acute bronchitis of four days' duration. The blood pressure was 200 systolic and 90 diastolic. The patient improved until Jan. 18, 1936, when a moderate swelling developed at the angle of the right jaw, tender and painful. Ice packs, oral hygiene and gum chewing were used, and the swelling subsided by January 23, five days after the onset.

CASE 16 (St. Mary's Hospital).—A white woman aged 32 entered on March 9, 1936, with a history of chronic otitis media on the left and acute bronchitis of ten days' duration diagnosed as bronchopneumonia. The white blood cell count was 15,600. The day after entry, March 10, a painful tender and marked swelling of the left parotid occurred. There was rapid enlargement of the gland, and pus was draining from the duct. The left gland was incised on March 11. It was swollen. There was no pus, but the gland was gangrenous. Culture showed *Staph. aureus*.



On the evening of March 11, the right gland rapidly enlarged and became tender. The temperature was 101 F. The white blood cell count was 25,000. A blood culture was negative. Within twenty-four hours there was rapid increase in the swelling with increase of temperature to 102 F. and of the white blood cell count to 35,000. The right gland was then incised in the same way; it was a dark slightly necrotic gland which on culture gave a growth of *Staph. aureus*. Following incision, the white blood cell count dropped to 14,000, and the glands drained thick pus for a week. In several days there were ulcers present in the mouth and swelling of the left submaxillary gland. When the submaxillary duct was opened, pus exuded; pus also drained from the left parotid duct. Two weeks after the glands were opened, a state of mental confusion developed, which was diagnosed as toxic psychosis. The parotid incisions were healed in four weeks, but the psychosis persisted for some time after the patient's discharge.

CASE 17 (St. Mary's Hospital).—A white woman aged 75 years with hypertensive cardiovascular disease with recent cerebral hemorrhage entered in uremic coma on July 11, 1936. The nonprotein nitrogen content was 100 mg. Urinalysis showed many cells, casts and albumin. Three days after entry, July 14, there occurred a gradually enlarging swelling of the right parotid. Ice packs were applied, but gradual enlargement continued so that by July 16 it involved the cheek and caused edema of the eyelids, also extending into the neck, resulting in difficult respiration and swallowing. The swelling had subsided somewhat when the patient died on July 19, five days after the onset.

CASE 18 (Firmin Desloge Hospital).—A white man aged 58 suffering from tertiary syphilis, pernicious anemia and advanced nephrosclerosis entered on Nov. 22, 1936, with orthopnea, dyspnea, edema of the extremities and painful joints of two weeks' duration. The nonprotein nitrogen content was 95 mg. On November 26, the patient became comatose and remained stuporous to the end. On December 16, a swelling began in the right parotid area, and ice bags were applied, but the edema and the inflammation were progressive so that by December 18 the gland was enormous, red and tender but not fluctuant. The mouth was filthy, with sores on the lips and the tongue, although mouthwash had been given routinely. A blood culture was negative, and a culture from the duct orifice yielded gram-positive cocci and gram-negative rods on December 20. Hot packs were applied, and the gland became fluctuant, but incision was refused. Seven days after onset, the parotiditis on the right began to subside while the left gland rapidly became swollen, and ice packs were applied. The culture from the left duct grew gram-positive cocci in clusters. The comatose state of the patient deepened on December 25, and he died. At no time did the patient's temperature go above 99 F.

CASE 19 (St. Mary's Hospital).—A white woman aged 42 with a history of severe sore throat, fever and chills entered Dec. 31, 1936, with a red injected pharynx and a coated tongue, but the teeth were in a fairly good state of repair. The white blood cell count was 14,000. A throat culture grew hemolytic streptococci. On Jan. 1, 1937, a small swelling began below and behind the right ear, and the face appeared red and swollen. In twenty-four hours a brawny edematous swelling was present, and the gland was incised and drained. A wound culture gave hemolytic streptococci. Ice bags were applied. Within forty-eight hours of the incision there was an erysipeloid rash at the site of drainage. The urine showed casts, albumin and cells. The temperature was 100.8 F. The parotid swelling subsided, but the erysipelas rash spread to the nose, the lips, down the neck to the scapular regions, the axillas and to the buttocks. Antiserums and convalescent

erysipelas serum were given, and magnesium sulfate packs were applied. The patient recovered and was discharged on January 22.

CASE 20 (St. Mary's Hospital).—A white man aged 60 years had pharyngitis, nodular goiter with auricular fibrillation and pneumonia in the upper lobe of the right lung of three days' duration. The temperature was 105 F. The white blood cell count was 31,000. A blood culture was negative. The patient received 40,000 units of antipneumococcic serum. The patient was weak and jaundiced on entry. On Jan. 27, 1937, parotiditis began on the right and rapidly developed, involving the whole side of the face and the neck. Mouthwash and gargles had been given continuously. Hot packs were applied. The patient died on January 28, within twenty-four hours of the onset of parotiditis.

CASE 21 (St. Mary's Hospital).—A white woman aged 29 with a history of bilateral mumps in childhood, rheumatic heart disease and Still's disease since 1931 entered with the diagnosis of Still's disease and acute secondary parotiditis on July 16, 1937. Her complaint was of painful joints and swelling in the left parotid of recent onset. The temperature was 103 F. The following day there was localization and brawny edema. The duct papilla was red, edematous and elevated, but no pus could be expressed. Ice bags were applied and mouthwash and gargle used. On July 18, with the patient under local anesthesia, the gland was incised transversely at the angle of the jaw. No pus was present, but cultures grew staphylococci. The white blood count was 6,700. Azosulfamide<sup>2</sup> (40 cc. intramuscularly in divided doses) and sulfanilamide (5 grains [0.32 Gm.] every four hours) were given. Twenty-four hours after incision, the swelling of the gland began to subside although respiration was difficult and the patient complained of pain in the back of the neck. On July 20, examination revealed bilateral maxillary sinusitis, more on the right than on the left. The gland swelling rapidly subsided, and the patient was discharged on July 22, six days after entry.

CASE 22 (Firmin Desloge Hospital).—A white man aged 73 entered in December 1937 with the complaint of urinary obstruction with acute retention. Examination revealed a large prostate with urethral obstruction. The patient had also far advanced cardiovascular disease with coronary sclerosis. On December 27, a small swelling occurred in the right parotid gland and was diagnosed as parotiditis. Ice packs were applied. The gland subsided in several days. The patient was found to have diabetes, and treatment was given. During January 1938, the patient had chills and high fever from pyelonephritis and cystitis. The patient was semi-comatose. On January 19, the right parotid gland again became swollen and tender, and ice packs were applied. The mouth was dry and coated, and the patient was a constant mouth breather. The duct and pus from the incised gland on culture showed *Staph. albus* and *Staph. aureus*. The gland subsided after incision and drainage on the third day after onset. The patient grew gradually weaker and died on the sixth day. The white blood cell count and the fever were high throughout the period of renal infection and so masked the true white blood cell count and fever from the parotiditis. No autopsy was performed.

CASE 23 (Firmin Desloge Hospital).—A white girl aged 13 with previous entries for severe hypertension and nephritis and possible bilateral polycystic kidneys entered on April 10, 1938, with air hunger, edema of the lower extremities

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2. Azosulfamide is disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxy-naphthalene-3',6'-disulfonate. This substance has been known as prontosil soluble, as prontosil and as neoprontosil.

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and hypertension. Examination revealed that there were a blood pressure of 200 systolic and 150 diastolic, a systolic heart murmur, secondary anemia, a nonprotein nitrogen content of 93 mg.; the urine gave a 3 plus reaction for albumin with many white and red blood cells. Retinal examination revealed albuminuric retinitis. The patient gradually became stuporous and drowsy, and on April 28 the non-protein nitrogen was 347 mg. The patient passed into uremic coma, and anuria developed. The blood pressure fell on May 1 to 134 systolic and 50 diastolic, and swelling of the right parotid developed, gradually becoming larger. The temperature was 100 F. A culture from the right duct on May 3 grew hemolytic gram-positive cocci in clusters and gram-positive rods. On May 3, the right-sided parotiditis had closed the eye. The patient was deeply comatose when she began having convulsions and died fifty hours after the onset of parotiditis. Autopsy revealed swelling in the right parotid area with tense skin and some reddening over the area. There was edema in all tissues with advanced nephrosclerosis.

CASE 24 (Firmin Desloge Hospital).—A white woman aged 59 entered on May 9, 1938, with a swelling of the left parotid area. The swelling began two weeks (April 25) before entry without apparent cause. At first, the swelling was soft and only slightly painful, but since then it had grown larger, harder and severely painful. One week after the onset, a sore throat and a cold developed. The pain increased on chewing and was referred to the ear. Examination revealed a swollen, tender, indurated, reddened area at the angle of the left jaw, about 4 by 3 by 2 inches (10 by 8 by 5 cm.) and not fluctuant. No stone was palpable or was seen by roentgen examination of the duct. All teeth had been removed years before. No pus was obtained from the duct. The white blood cell count was 10,000; the temperature was 100.2 F. The urine gave a 3 plus reaction for sugar. The blood sugar was 247. On May 10, with the patient under anesthesia induced with ethylene, a needle was inserted into the gland and pus found, and the gland was then incised, freeing 1 ounce (29.5 cc.) of pus, which on culture grew nonhemolytic streptococci. Moderate drainage continued until May 17, and the swelling rapidly subsided. The patient was treated and instructed regarding her diabetic condition, which was found on entry, and was discharged May 21.

*Thirty-two cases accompanying surgical conditions*

CASE 25 (St. Mary's Hospital).—A white woman aged 29 was operated on Sept. 23, 1924, and a subacutely inflamed gallbladder with stones was removed. On the second postoperative day, a small swelling of the right parotid occurred, and ice packs were applied. The temperature rose from 100 to 101 F. The white blood cell count was 15,800. In twenty-four hours, the left gland was swollen, painful and tender, and ice was applied to both glands. The left gland subsided, but the right gland went on to fluctuation and was incised nineteen days after onset by a vertical incision just anterior to the ear, freeing pus, which on culture yielded staphylococci. The gland drained abundantly, and there was still some drainage when the patient was discharged on October 21, twenty-six days after onset.

CASE 26 (St. Mary's Hospital).—A white woman aged 57 was operated on for chronic duodenal ulcer, and a posterior gastroenterostomy was done Sept. 28, 1926. Although apparently adequate fluid was given, the patient complained of marked thirst and pain in her throat on the second postoperative day. In another twenty-four hours (October 1), the right parotid gland was swollen, tender and painful, and the right seventh cranial nerve was paralyzed. Ice packs and oral hygiene were used, but the gland was so swollen that an incision was made. The gland was gangrenous, and there was some pus, which on culture grew Staph. albus.

The white blood cell count was 17,000. The temperature was 102 F. On the fourth day of parotiditis (October 4), the temperature had fallen, but there was black slough at the bottom of the wound. Hot packs were applied. On October 6, there was sloughing of glandular tissue. On the tenth day of parotiditis, the skin wound and much of the gland were necrotic. Two small fluctuant areas were incised and the wound irrigated with diluted solution of sodium hypochlorite (Dakin's solution). On the fourteenth day following incision, the sloughing of skin and the gland was marked. On the eighteenth day after onset, there was extension of the inflammation into the posterior triangle of the neck near the mastoid process, requiring incision two days later. Sodium perborate irrigations were used. On the nineteenth day after the first incision, the patient was up, and there had occurred sloughing of the gland. The patient's temperature ranged from 99 to 101 F. during her convalescence. The patient remained in the hospital three weeks longer, but the wound had not completely healed on discharge. The paralysis remained.

CASE 27 (St. Mary's Hospital).—A white woman aged 26 had curettage for retained secundae on March 3, 1927, and uterine suspension on March 7. On March 9, twenty-four hours after operation, the patient complained of pain in the left ear, and several hours later a swelling was noted in the left side of the face. She also complained of difficulty in swallowing. The temperature rose from 99 to 103 F. Ice bags and gargles were used from the onset. By the fourth day, the swelling extended into the neck. The mass was tender, and the skin was edematous and red-blue. The white blood cell count was 25,800. With the patient under anesthesia induced with ethyl chloride, the gland was incised widely by a Y incision, freeing pus and necrotic glandular tissue. A culture grew *Staph. albus*. Heat was applied to the gland after drainage. Six days after drainage, inability to close the eye and left facial weakness were noted, but these had disappeared in a week. Some time during the course of the infection, pus ruptured into the external auditory canal. There was slight drainage from the gland when the patient was discharged on April 8. Repeated blood cultures were negative.

CASE 28 (St. Mary's Hospital).—A white woman aged 55 entered on Aug. 15, 1929, with her left hand swollen to twice the normal size and excruciatingly painful following a pinprick, resulting in tenosynovitis and palmar bursitis. The area of abscess was incised and drained and three days later the tendon sheaths were incised. On August 30, the patient's temperature rose from 100 to 102 F., as a large rapidly increasing inflammatory swelling occurred in the left parotid area and the neck. The white blood cell count was 16,000. Oral hygiene was satisfactory. The enlargement of the parotid increased in the next twenty-four hours, and a swollen edematous gland was opened by an incision below the ear and forward parallel with the mandible for 2 inches (5 cm.). The gland later drained pus profusely and decreased in size, but the wound was still draining when the patient was discharged.

CASE 29 (St. Mary's Hospital).—A white man aged 23 known to have diabetes entered on May 5, 1933, with a blood sugar content of 333 mg. and peritonitis and a large mass in the right lower quadrant of the abdomen. The white blood cell count was 17,700. The patient was operated on; a ruptured appendix was removed, and an abscess was drained. On May 8, the third postoperative day, a painful swelling occurred at the angle of the right jaw, and ice packs and oral hygiene were instituted. In twenty-four hours, the swelling had increased markedly, was tender and painful and caused stiffness of the neck. The temperature was 102.6 F. After forty-eight hours, the gland was drained by an incision below

the ear and along the mandible, where the swelling was greatest. No pus was found. On May 11, the third day of parotiditis, there was edema of the entire right side of the face and both eyelids, and on the fourth day, the uvula was edematous. Thereafter, the inflammation rapidly subsided, and the patient was discharged on June 3 with the wound practically healed. The parotid was less responsible for the delayed discharge than the draining abdominal wound.

CASE 30 (St. Mary's Hospital).—A white woman aged 53 was operated on on Sept. 26, 1933. Appendectomy and hysterectomy were done. On the tenth day after operation, parotiditis developed rapidly on the right side. The white blood cell count was 36,600. The temperature was 101.4 F. After twenty-four hours, the gland was incised and drained, but no pus was found. Within two days, the parotiditis had subsided. The white blood cell count was 12,600. The temperature was 103 F. A blood culture was negative. On the sixth day, the patient's temperature was normal. A week after the parotiditis had subsided, the abdominal wound was opened and drained urine. The patient later recovered entirely.

CASE 31 (Firmen Desloge Hospital).—A white woman aged 36 entered on Nov. 26, 1933, and on December 9, at operation, a ruptured ectopic pregnancy was found. On the fifth postoperative day, a swelling developed in the left parotid, which rapidly involved the whole gland, with pain in the ear, and the temperature rose to 102 F. In forty-eight hours, a small incision was made below the left ear, freeing pus which cultured *Staph. albus*. The white blood cell count was 12,000. The same evening, the patient complained of pain and tightness in the throat with inability to open the mouth. The gland remained swollen, and hot packs were applied. Five days after the first incision, the gland was re-incised by an inverted T incision, opening an extracapsular and intracapsular abscess which had burrowed back to the external auditory canal. The neck of the mandible was surrounded by an abscess cavity containing 3 ounces (88.7 cc.) of pus. There was also a hard phlegmon of the gland along the head of the mandible and behind the ear. During the operation, the abscess ruptured into the mouth. The temperature was 101 F. There were abundant drainage from the incisions and marked sloughing of the gland followed by seventh nerve paralysis. On Jan. 7, 1934, an abscess was found on the anterior part of the gland and was incised the next day. The patient complained of severe headache and occipital pain on the same side as the parotiditis. Pus was draining from the ear, both from the parotid extension and from suppurative otitis media. The patient continued to complain of terrific pain in the head, and temporal abscess was suspected. On January 27, a prominence of the eyes was noted, more on the right than on the left. On January 28, the right eye was protruding, and the patient was complaining of photophobia and occipital pain. After three days, the temperature was 103.8 F., and the patient became irrational and incoherent. The patient was operated on for disease of the mastoid, and acute purulent infection was found in the mastoid. The patient died fourteen hours later. Autopsy revealed acute purulent sphenoid and ethmoid sinusitis, otitis media, cavernous sinus thrombosis, septic pneumonia and septic necroses in the liver and the kidneys. The necrotic wound of the parotid showed pus deep in the cavity, and palpation revealed the bare temporomandibular joint and an abscess cavity extending upward and medial to the mandible.

CASE 32 (St. Mary's Hospital).—A white woman aged 23 had her tonsils removed on Aug. 15, 1934. This was followed five days later by a swelling in the parotid on the left. On entry, August 26, the patient complained of pain in the throat and of a large, red, hot, painful, nonfluctuant swelling of the left parotid.

The patient could not open her mouth. Ice packs were applied and fluids forced until August 30, ten days after the swelling started, and then with the patient under local anesthesia the gland was incised by a vertical incision in front of the ear, freeing yellow pus. Four days later there was rupture of pus into the external auditory canal. The edema and swelling rapidly subsided, but the patient complained of pain and swelling in her throat, and on September 14, two weeks after the gland was drained, a peritonsillar abscess was opened and an impacted molar tooth extracted. The patient was discharged on September 19, twenty-three days after entry.

CASE 33 (St. Mary's Hospital).—A white woman aged 31 entered for cholecystectomy. This was done on Dec. 5, 1934. On the sixth postoperative day, the patient complained of dryness of the mouth and pain in the right parotid, which rapidly became swollen, red and tender. The white blood cell count was 19,700. The temperature was 100.2 F. In three days there was increased swelling, and the skin of the right side of the face was tense. The gland was tender but not fluctuant. The duct was slightly red and swollen, with a drop of pus at the orifice; cultures of the pus grew *Staph. albus* and small gram-positive rods. The gland was incised under local anesthesia by a vertical incision, freeing no pus but, on culture, growing *Staph. albus*. Hot packs replaced the ice which had been applied to the gland. The white blood cell count was 33,000. There was gradual improvement and abundant purulent drainage in forty-eight hours. The patient was discharged December 30, sixteen days after the onset of parotiditis.

CASE 34 (Firmen Desloge Hospital).—A young white man aged 18 was struck on the side of the face by a fist; this was followed forty-eight hours later by a rapidly developing swelling of the face, the cheek and the upper part of the neck. On entry, Nov. 1, 1934, twelve days after injury, the condition was diagnosed as fracture of the mandible and parotid abscess on the left. The area was red, hot and tender with generalized swelling of the left cheek and extension of the swelling into the neck. The overlying skin was tense, smooth and shiny. The white blood cell count was 14,000. The temperature was 102 F. Soon after entry, with the patient under anesthesia induced with nitrous oxide, the abscess of the parotid was opened by a 2 inch (5 cm.) incision along the ramus of the mandible, and a rubber dam drain was inserted. A large amount of pus, white in color and foul in odor, was freed. Smears made from the pus showed organisms of Vincent. Hot wet packs were applied to the wound, and the temperature fell to normal within twenty-four hours. The patient was discharged ten days after the incision of the gland.

CASE 35 (Firmen Desloge Hospital).—A white man aged 70 years entered Nov. 21, 1934, for fulguration of a squamous cell carcinoma on the right side of the hard palate. Extensive fulguration was done, including the soft palate, and nasal tube and intravenous feeding was necessary. Because of unhealthy gums and teeth, mouthwash was used frequently. Five days after operation, November 27, bilateral swelling appeared in the parotid region, more on the left than on the right, and ice packs were applied. The swelling of the left gland continued to increase, and after seven days, with the patient under local anesthesia, an abscess of the left parotid was opened by an incision 2 inches (5 cm.) long below and parallel to the body of the mandible. Culture from the wound grew gram-positive cocci. The left parotid subsided after the incision. Sixteen days after the swelling first appeared in the left gland, the right gland became markedly swollen and was incised the following day by a 1 inch (2.5 cm.)



incision obliquely placed behind the angle of the jaw. The capsule was opened, freeing thick yellow pus, which on culture grew gram-positive cocci in clusters. In one month, the left parotid was healed, and the right had subsided. The patient was discharged on December 23.

CASE 36 (Firmin Desloge Hospital).—A white woman aged 44 with uterine carcinoma, carious teeth, pyorrhea alveolaris and pharyngitis was operated on. A radical Wertheim procedure was done. Six days after operation, a small stitch abscess was opened. The patient had a chill. The temperature was 103.6 F. The white blood cell count was 25,000. Cystoscopic examination showed cystitis and pyelitis. A culture of the abdominal wound showed gram-positive cocci in clusters and *Bacillus coli*. On forced fluids, transfusions and sustaining treatment, the patient improved. On Oct. 18, 1936, the twenty-second postoperative day, the patient noticed a tender swelling below the right ear and behind the angle of the jaw. The temperature rose from 99.8 to 101.2 F. In twenty-four hours, the swelling had greatly increased and was painful and tender. The papilla was red and elevated, but no pus could be expressed from the duct. Ice packs, oral hygiene and chewing gum were given. On the third day, with the patient under anesthesia induced with ethylene, a 3 inch (7.6 cm.) vertical incision was made just anterior to the ear. No pus was found, but cultures grew gram-positive cocci and gram-negative rods. Blood cultures were negative. In two days, the gland swelling subsided. In twelve days, the temperature and the white blood cell count were normal, and the gland was healing. The wound was entirely healed on the twenty-sixth day.

CASE 37 (St. Mary's Hospital).—A white woman aged 59 had a panhysterectomy done for carcinoma of the cervix on March 23, 1936. On the sixth postoperative day, the left parotid became enlarged. Ice packs were applied, but in twenty-four hours, the swelling had increased, and the right parotid was beginning to swell also. The temperature was 100 F. The white blood cell count was 21,500. Oral hygiene was given. The pain was severe and the swelling marked, but the right gland was subsiding on the third day\* (April 1). The left gland was drained by a small incision with the patient under local anesthesia, and the swelling gradually subsided. Discharge from the gland was slight, and the gland was healing by April 3. On April 14, seventeen days after the onset, a reddened area appeared at the left ear, became fluctuant and was incised on April 16. Recovery was gradual, and the patient was discharged on May 18.

CASE 38 (St. Mary's Hospital).—A white woman aged 45 was operated on for fibromyoma of the uterus on April 3, 1936. On April 7, signs of peritonitis developed, and the wound on culture gave a growth of streptococcus. The same day, a firm swelling developed in the parotid, not red or tender. The white blood cell count was 9,500. The temperature was 103 to 104.5 F. The condition was diagnosed as acute peritonitis and secondary parotiditis. Within twenty-four hours, the gland was incised, but no pus was found, although cultures showed staphylococci. The urine showed albumin and red cells. Peritonitis was progressive, and the patient died on April 10. The gland swelling had subsided before death. No autopsy was done.

CASE 39 (St. Mary's Hospital).—A white woman aged 46 was operated on June 16, 1936. Total hysterectomy, oophorectomy and appendectomy were done. After seven days, the white blood cell count was 20,000. The temperature was 102 F. An abscess of the abdominal wound was opened, and cultures grew gram-negative cocci and bacilli and gram-positive cocci. On June 27, the eleventh post-

operative day, parotiditis began on the left side at the angle of the jaw, and the swelling occurred so rapidly that in twelve hours the whole side of the face and the upper part of the neck were involved—there was even edema of the eyelids. Ice packs, lemon juice, chewing gum and gargles were given. The gland was exquisitely tender. In twenty-four hours, the edema of the eyelids was marked, and the skin of the left side of the face was red, brawny and edematous. On June 28, with the patient under general anesthesia, the gland was opened; it was black and gangrenous. Culture showed *Staph. aureus*. Blood cultures were negative. Hot boric acid packs were applied. The next day, the edges of the wound were necrotic; the gland was a dirty gray color, and the patient was growing weaker. In the next four days, the swelling slowly decreased, and pus began draining through the ear on July 3. The temperature was 102 F. On July 4, a pelvic abscess was opened through the vagina. Thirty minutes after opening the pelvic abscess, the patient suddenly died. No autopsy was performed.

CASE 40 (St. Mary's Hospital).—A white woman aged 85 entered on Aug. 9, 1936, in a critical condition with pain and a mass in the right upper quadrant of the abdomen present for five days before entry. The white blood cell count was 30,000. The temperature was 101 F. The patient was treated conservatively until August 15. With the patient under local anesthesia, acute empyema of the gallbladder with stones and local peritonitis was drained. A culture of the gallbladder grew *B. coli*. The same evening, the left parotid began to enlarge and in a few hours involved the side of the face and the neck. Previous to operation, little fluid had been taken per os, the patient receiving fluids parenterally. After twenty-four hours, with the patient under local anesthesia, the left gland was opened by a vertical incision anterior to the ear. The gland was necrotic and green-gray. Three days after the onset of parotiditis, the patient complained of difficult swallowing and sore throat, and a swelling of the right submaxillary gland was noted but gradually subsided in three days. The left parotid gradually decreased in size, but the patient grew weaker, and cardiac failure and auricular fibrillation developed. The patient died on August 27, eleven days after the onset of parotiditis. No autopsy was done.

CASE 41 (St. Mary's Hospital).—A white woman aged 50 had mastoidectomy on the left on Sept. 2, 1936. On September 14, a rapidly increasing swelling occurred at the angle of the left jaw, and a slight enlargement of the right parotid also appeared. On entry, September 15, the left gland was firm, tender, non-fluctuant and painful, especially on opening the mouth. The temperature was 100.6 F. The white blood cell count was 11,900. Ice packs were applied to both glands, and the swelling decreased in four days. When the patient could open her mouth, carious teeth, injection of the pharynx and poor oral hygiene were noted. The patient was discharged on September 20, six days after onset of parotiditis.

CASE 42 (Firmin Desloge Hospital).—A white woman aged 26 had the right lower first molar extracted, and three days later, on Feb. 9, 1936, swelling began in the right parotid area just anterior to the ear and rapidly increased until the patient could open her mouth to the extent of only 1 cm. When she entered on February 18, nine days after onset, the swelling was painful and tender, extending from the zygoma to 1 inch (2.5 cm.) below the angle of the jaw and 2 inches (5 cm.) anterior to the ear with the skin brawny and edematous. The gums were covered with a white membrane which left a bleeding area when removed. The duct was not red or elevated. The temperature was 103 F. The white blood

cell count was 17,500. In twenty-four hours, the right eye was entirely closed by swelling and edema, which extended also several inches below the angle of the mandible. Smears from the gums showed no spirilla. In another twenty-four hours, the right side of the face drooped from facial nerve weakness, and respiration and swallowing were difficult. On March 1, twenty-one days after onset, the gland was incised from below the ear forward, freeing a large amount of pus, foul smelling but growing no organisms when cultured, although the right duct on culture now yielded a growth of fusiform bacilli. The abscess had almost completely destroyed the gland and extended into the retromandibular space. Hot packs were applied. The swelling decreased, and the fever fell to 101 F., but forty-eight hours after incision the temperature rose to 105.6 F., and there was evident extension down into the anterior and posterior triangles of the neck. There was extensive necrosis deep in the wound. Diluted solution of sodium hypochlorite (Dakin's solution) was used for irrigation on the fifth day. The white blood cell count was 27,000. Septic fever was present with a temperature as high as 106.5 F. On the sixth day, March 7, a 2 inch (5 cm.) incision was made above the clavicle, freeing a large amount of foul pus from a cavity beneath the cervical fascia. The patient was toxic and weak. Transfusions were given. On March 9, eight days after the gland was first incised, a moderate second degree hemorrhage occurred in the retromandibular space. The patient died on March 10. All blood cultures were negative. No autopsy was done.

Such a history does not reflect credit, but it must be taught that when acute surgical parotiditis develops, it requires the services of a properly qualified surgeon.

CASE 43 (Firmin Desloge Hospital).—A white woman aged 48 had cholecystectomy and appendectomy done on June 15, 1936. On the third postoperative day, the temperature rose to 101 F., and swelling began in the regions of both parotids. The patient had been on a liquid diet for some days. In twenty-four hours, the temperature rose to 104 F., and the right gland increased in size rapidly, involving the face and the neck to such an extent that dyspnea was marked, and a tracheotomy tube was kept in the room. The white blood cell count was 19,000. The left parotid also was hard and edematous. Forty hours after onset, on June 20, with the patient under local anesthesia, a 2 inch (5 cm.) incision was made bilaterally, extending from the tragus down and forward over the gland. Culture of the gland showed *Staph. aureus*. There was no pus. Difficulty on swallowing and swelling of the gland continued until June 26, when pus ruptured into the right external auditory canal, and then the swelling and the fever subsided. Within four days, all symptoms had subsided. The parotid wounds were healing when the patient was discharged on July 15, on the twenty-seventh day after the onset of parotiditis.

CASE 44 (Firmin Desloge Hospital).—A white man aged 31 was operated on July 18, 1936 for what was thought to be a perforated gangrenous appendix (later it proved to be a perforated cecal diverticulum), and a large abscess cavity was drained. On July 21, the third postoperative day, the right parotid gland became swollen. The temperature rose from 101 to 104 F. Ice packs were applied, and oral hygiene was given, but the swelling increased and within forty-eight hours extended to the clavicle and was exquisitely tender. The white blood cell count was 21,000. The patient had chills. The gland was opened by a linear incision in front of the ear and at the angle of the jaw, freeing a bloody fluid. A culture

of the gland was negative, and a blood culture was negative. On the third day, the parotid and the cervical fascia were divided because of extreme swelling. The swelling decreased, and by July 25 (the fourth day) there was abundant purulent drainage, which on culture gave a growth of *Staph. aureus* and *Staph. albus*. The temperature was 102.5 F. Rales were present in the lungs. By July 27, the swelling had increased to almost midline and 2 inches (5 cm.) below the clavicle. Incision was made below the clavicle, draining a pocket of pus. Pus had burrowed back to the mastoid and along the mandible to the midline. On July 28, the anterior triangle of the neck was opened widely, and the jugular vein was ligated. The swelling had increased to the point that breathing was difficult. Following a transfusion, the patient had a chill, and the temperature rose to 106.4 F. He died two hours later. Autopsy revealed red, edematous swelling of the entire right side of the face and the neck with pitting edema. Septic pneumonia and general toxic changes in all viscera were present.

CASE 45 (Firman Desloge Hospital).—A white woman aged 71 with marked arteriosclerosis and hypertension and inoperable carcinoma of the sigmoid colon had a colostomy done July 31, 1936. Fluids were not withheld, and mouthwash was frequently given. On the fourth postoperative day, the right parotid began to swell, becoming red, firm and tender, painful and hot. The white blood cell count was 20,000. The temperature was 100 F. Within twenty-four hours, with the patient under general anesthesia, the gland was drained by a vertical incision anterior to the ear. The gland was red and edematous and on culture grew *Staph. aureus*, but no pus was present in the gland. Hot packs were applied. On the second day of parotiditis, respiration was difficult, and the patient was weak. Signs of acute cardiac failure developed rapidly. On the fourth day, the right gland was subsiding when swelling of the left gland occurred and advanced so rapidly that within twenty-four hours the entire left side of the face and the neck was involved. Respiration was so difficult that a tracheotomy set was kept in readiness. A wide incision was made from the zygoma to well below the mandible, just anterior to the ear. The patient became comatose and died on August 8, on the fourth day of parotiditis and eight days after operation. No autopsy was done.

CASE 46 (Firman Desloge Hospital).—A white man aged 24 entered with a history of no bowel movements in seven days and with a rigid silent abdomen and picture of marked toxicity. At operation a ruptured appendix was removed. General peritonitis was present and, in addition, there were five points of obstruction of the small bowel and volvulus of the entire small intestine and its mesentery. One area of the ileum was gangrenous and was brought on the surface of the abdomen. The patient went into shock but recovered. Subsequently, he recovered sufficiently for repair of the ileostomy and resection of a portion of the small bowel. This was done on Dec. 16, 1936, two months after the first operation. On the third day after this operation, swelling occurred in both parotids, and ice packs were applied. The swelling increased rapidly on the right and soon extended from the zygoma to below the angle of the jaw and 2 inches (5 cm.) anterior to the ear. Both parotids were tender, but the right was brawny, and the overlying skin was tense and shiny. Cultures of the right duct showed *Staph. aureus* and gram-positive rods, and cultures of the left duct, *Staph. aureus*. The white blood cell count was 13,000. The temperature was 99.6 F. After twenty-four hours, the right gland was opened widely by a vertical incision with the patient under local anesthesia. No pus was found, but the gland was acutely inflamed. The left gland increased in size but gradually subsided under ice packs and azosulfamide.

In eight days both glands were back to normal size, and the right parotid was healing when the patient was discharged on Jan. 7, 1937, three weeks after onset of parotiditis.

CASE 47 (Firmin Desloge Hospital).—A white woman aged 61 with pyloric obstruction due to carcinoma of the stomach had a gastroenterostomy done on Nov. 16, 1936. The patient insisted on wearing her dentures after operation and it was difficult to maintain good oral hygiene. On the fifth postoperative day, November 21, the patient's temperature rose from 99 to 101 F., and a swelling appeared at the angle of the left jaw. Ice packs were applied to the gland, and lemon juice, chewing gum and gargles were given. The swelling increased slowly, and by the third day it was 2 by 2 inches (5 by 5 cm.), lying beneath the ear and on the mandible at the angle. The duct was normal. In another thirty-six hours, on November 26, the swelling extended from the zygoma to 2 inches (5 cm.) below the mandible and from the mastoid to 2 inches (5 cm.) anterior to the ear, with brawny edema of the area. The white blood cell count was 10,000. On November 27, the gland was tense and red but not fluctuant, and it was incised with the patient under local anesthesia by a vertical incision anterior to the ear and a short horizontal incision along the ramus of the mandible. The gland was red-brown and showed marked inflammatory edema, but no pus was present. At this time (sixth day), pus was exuding from the duct on pressure on the gland. Cultures of the duct and the gland gave a growth of staphylococcus. The white blood cell count was 17,000. As the gland began draining pus, the edema and the inflammation subsided, and a facial weakness present for several days before incision gradually disappeared. The gland drained a week, when a tender painful swelling occurred at the mastoid, and pus was draining from the external auditory meatus. The small abscess beneath the ear in the mastoid area was incised, and about 10 cc. of pus was evacuated. Both wounds healed by granulation, and the patient was discharged on December 16, three weeks and four days after the onset of parotiditis.

CASE 48 (St. Mary's Hospital).—A white man aged 28, entered in shock and was operated on for perforated gastric ulcer on Nov. 16, 1936. Perforation had occurred nearly twenty-four hours before entry, and general peritonitis was present. Oral fluids were given regularly. On the ninth postoperative day, the white blood cell count was 14,500. The temperature was 102 F. A small swelling appeared at the angle of the left jaw just below the ear; the area was red, firm and tender. Ice packs were applied, and mouthwash, lemon juice and potassium iodide (15 grains [0.97 Gm.] three times per day) were given. The following day, the patient felt secretion passing into his mouth on the left side, relieving the pain and decreasing the mass slightly. The duct papilla was red and edematous, and there was dirty gray coating on the teeth and gums. Culture from the left duct grew gram-positive cocci and rods and gram-negative rods. The gland enlarged, and hot packs were applied. A 30 per cent erythema skin dose of roentgen radiation was given to the left gland on December 1, five days after the onset of parotiditis. Pus was draining from the ear and through an opening in the anterior wall of the external auditory canal. The pus when cultured yielded a growth of *Staph. aureus*. Blood cultures were negative. On the sixth day, the gland was incised and drained of pus which on culture gave *Staph. aureus*. The swelling and the drainage subsided, and the temperature dropped from 103 to 99 F. in a week. On December 9, two weeks after the onset of parotiditis on the left, a swelling of the right submaxillary gland was noted. The submaxillary became fluctuant after nine days, and the gland was incised on December 18. On December

22, the patient was operated on for intestinal obstruction due to massive peritoneal adhesions, and when reobstruction occurred on December 26, a Witzel enterostomy was done. The parotid and the submaxillary glands were entirely healed before the second operation for obstruction. The patient continued to grow weaker and died on Jan. 22, 1937, nearly two months after the onset of parotiditis. Autopsy showed gangrene and multiple perforation of the small bowel with multiple abscesses.

CASE 49 (Firmin Desloge Hospital).—A white man aged 33 with untreated diabetes mellitus and bilateral apical tuberculosis had the right lower second molar tooth extracted on Dec. 20, 1936. Six days later a gradual swelling, painful and tender, developed in the right parotid area. Three days later, the patient had a chill, and he had difficulty in swallowing and opening his mouth due to the brawny swelling. The patient entered on December 31, the fifth day of parotiditis, with a red tender fluctuant swelling of the right parotid extending from the zygoma to 3 cm. below the angle of the mandible. The blood sugar was 365 mg. The white blood cell count was 14,700. The temperature was 99.2 F. The gland was drained soon after entry through a 2 inch (5 cm.) incision vertically and just anterior to the ear, and a 2 inch (5 cm.) incision at the angle of the jaw, freeing 30 cc. of foul pus. Oral hygiene and hot packs were used, and the gland drained freely. Blood and wound cultures were negative. The patient was discharged to the clinic with an unhealed wound on Jan. 15, 1937, three weeks after onset.

CASE 50 (St. Mary's Hospital).—A white woman aged 33 had a criminal abortion performed by a midwife on Dec. 4, 1936, and was well until December 19, when symptoms of peritonitis developed. The patient entered the hospital on December 22 with a rigid tender abdomen. On December 29, the white blood cell count was 10,500. The temperature was 99.6 F. A swelling began in the right parotid followed soon by an enlargement of the left gland. The temperature rose to 101.2 F. In twenty-four hours there was marked increase in the swelling with the left side edematous to the eyelids but the right side more brawny, edematous and painful. A 30 per cent erythema skin dose of roentgen radiation was given to the right gland on December 31. The left gland subsided without further interference. Azosulfamide was given seventy-two hours after the onset of parotiditis, and a second roentgen treatment was given on Jan. 2, 1937. The white blood cell count was 22,000. On January 4, the twelfth day of parotiditis, there was fluctuation at the level of the angle of the mandible, and with the patient under local anesthesia a wide Y incision was made, freeing pus from an abscess at the lower pole of the right gland. The gland was black and necrotic; cultures from it grew *Staph. aureus*. After two weeks, the inflammation had subsided, and secondary closure of the incision was made. The patient was discharged on January 26.

CASE 51 (St. Mary's Hospital).—A white woman aged 47 entered with signs of peritonitis and paralytic ileus and was operated on for a ruptured diverticulum of the colon with abscess. A stormy postoperative course followed with the occurrence of fecal fistula. One month after the operation, a tender hard mass developed in the right parotid area and rapidly became swollen and brawny. The mouth was dirty with several badly decayed teeth. After twenty-four hours, the gland was opened by a vertical 2 inch (5 cm.) incision in front of the ear. No pus was present, but the culture grew *staphylococcus*. The gland drained several weeks, during which a psychosis developed, and the wound was healed by Oct. 10, 1937, four weeks after the onset of parotiditis.

CASE 52 (St. Mary's Hospital).—A white man aged 30 entered and was operated on Sept. 18, 1937, a ruptured appendix being removed and diffuse purulent peritonitis drained. Culture of the wound yielded gram-positive cocci and rods and gram-negative rods. On the fourth postoperative day, a sensitive swelling began in front of and just below the right ear. The patient was weak and toxic following operation and mentally dull. The temperature was 104 F. Ice packs were applied, and oral hygiene was given. By the sixth day of parotiditis, the swelling had extended into the neck, and the patient had difficulty opening his mouth. The white blood cell count was 9,900. On September 30, the eighth day, with the patient under local anesthesia, an extensive Y incision was made, freeing much pus and revealing a necrotic gland with a sinus extending into the external auditory meatus. A culture of the gland grew *Staph. aureus*. Hot packs were applied. The patient continued on a downward course and was irrational and weak. The white blood cell count dropped to 2,700. The patient died on October 8. No autopsy was performed.

CASE 53 (Firmin Desloge Hospital).—A white woman aged 46 entered Sept. 12, 1937, with a fluctuant swelling of the left parotid area diagnosed as parotid abscess. A small stone was palpable in the left parotid duct. The patient gave a history of previous swelling of the gland; this had subsided some months before entry. Six days before the patient came to the hospital, a painful enlargement of the left parotid began. Soon after onset, the patient noticed yellow semipurulent discharge in the region of the duct and found that the flow was increased by applying pressure on the parotid swelling. On entry, six days after the onset, the bulging left parotid area was firm, brawny and painful but not red, and the swelling extended from the lobe of the ear to the angle of the mouth and from the zygoma to below the mandible. There was some sign of fluctuation. The temperature was 103 F. The white blood cell count was 15,750. The papilla of the left parotid was red and edematous, and cultures of it grew gram-positive rods.

On the day of entry, the gland was drained by a 1½ inch (3.8 cm.) curved incision just anterior to the ear, and the capsule was opened, freeing 12 cc. of yellow foul-odored pus. The duct was incised, and a hard yellow stone about 3 mm. in diameter was removed. A rubber dam drain was used in the gland. Hot saline packs were applied to the gland, and mouthwash was given. Cultures from the gland grew large gram-positive rods, gram-negative rods and diplococci. A blood culture was negative.

After four days there was still profuse drainage, but the swelling had extended to the mastoid region with marked tenderness but no fluctuation in the area. On the sixth day after entry, September 18, the gland was reopened, carrying the first incision down and back under the ear, opening a large multilocular abscess. Culture showed the organisms of Vincent's infection, and the patient was given two doses of neoarsphenamine (0.3 Gm., three days apart). The discharge and the swelling decreased; the temperature fell, and the white blood cell count gradually returned to normal. The patient was discharged on the eighteenth day after entry, September 30.

CASE 54 (Firmin Desloge Hospital).—A white woman aged 61 with multiple fibromyoma of the uterus and carcinoma of the rectum was operated on on Nov. 19, 1937, and supravaginal hysterectomy and sigmoid colostomy were done preparatory to the removal of a rectal carcinoma. On the fourth day after hysterectomy and colostomy, a swelling appeared at the right parotid area, extending below the mandible, with red and firm overlying skin. The temperature was 102.5 F. The white blood cell count was 17,000. In twenty-four hours, the gland was greatly

swollen, carrying the ear outward from the side of the head. The duct was red and edematous, with a drop of pus at the orifice; the mouth was dry, and the teeth were dirty and carious. The gums were dirty and spongy, and the breath was foul. Ice packs were applied, and oral hygiene was given. Signs of peritonitis developed on the fifth postoperative day, and the temperature rose to 103 F. Cardiac fibrillation began. Blood cultures were negative, and a duct culture grew staphylococcus. The gland was subsiding when the patient passed into coma and died on the sixth postoperative day and the third day of parotiditis. No autopsy was performed.

CASE 55 (St. Mary's Hospital).—A Hawaiian-Chinese woman aged 23 entered May 12, 1938, with severe headache and pain in the right lower quadrant of the abdomen accompanied by nausea. The white blood cell count was 21,000, with 3 juvenile forms, 18 stab forms, 59 neutrophils and 20 lymphocytes. The blood chemistry and the hematologic findings were otherwise negative. With the patient under spinal anesthesia on the day of entry, the abdomen was explored and appendectomy done. The bowel and the peritoneum were red, and there was an odorless exudate present. The appendix showed catarrhal appendicitis. The abdomen was drained, and cultures from the exudate at operation were negative. On the third postoperative day, a blood culture grew hemolytic streptococci, and a pure growth of hemolytic streptococci was cultured from the drainage from the abdomen. The patient's temperature was 103 F. Fluids were forced intravenously, and antistreptococcic serum and antierysipelas serum was given. The patient was making gradual recovery until May 25, when she complained of pain in the left jaw; examination revealed a lower third molar cutting through the gum. The pain was attributed to this, but on the following day, May 26, a tender, tense and painful swelling developed in the left parotid. Ice bags were applied, and chewing gum was given. On May 27, the area was inflamed, and the papilla was inflamed with a deposit of flaky material around it. The temperature was 101.4 F. per rectum. The white blood cell count was 20,000. On May 28 the swelling continued, and ice packs were changed to hot boric acid packs. Culture made from the papilla grew nonhemolytic streptococci and *Staph. aureus*. The left gland was incised on May 28, and the whole gland was semicarcinomatous with an abscess behind the neck of the mandible, containing yellow odorless pus, which, on culture, grew *Staph. aureus*. Culture of the abdominal wound at this time yielded *B. coli*. After incision, hot wet 2 per cent saline packs were used. The temperature May 28 was 103.2 F. and by May 30 was only 100.6 F. per rectum. The gland continued moderate purulent drainage for three weeks and was irrigated with hydrogen peroxide and solution of sodium chloride until June 12. On July 28 there was thick purulent discharge from the left ear; this was diagnosed as otitis media. On August 4, acute hemorrhagic nephritis developed, and frequent transfusions were given. The patient recovered sufficiently to be discharged on September 25. At the time of writing, she remains well.

CASE 56 (St. Mary's Hospital).—A white woman aged 25 entered Nov. 19, 1938, with acute pain, nausea and vomiting diagnosed as acute cholecystitis with lithiasis. She was treated conservatively, and operation was deferred until December 5 because severe sinusitis, pharyngitis and bronchitis developed. On December 5, with the patient under spinal anesthesia, an acute subsiding inflamed gallbladder with stones was removed. On December 7, on the second postoperative night, the patient began to complain of pain in the jaw, and ice bags were applied. On December 8, a swelling began in the right parotid. Chewing gum and cleansing mouthwash were given. There was continued swelling of the gland, and the



temperature was up from 99 to 101.2 F. On December 9, the patient complained of pain and fulness in the throat. The temperature was 101.6 F. With the patient under anesthesia induced with cyclopropane, the gland was incised by a Y incision. The gland was found to be swollen, edematous and filled with a cloudy exudate which on culture yielded *Staph. aureus*. Sulfanilamide was given (30 grains [1.94 Gm.] daily for two days). On December 12, the face was still swollen on the right, and a slight swelling was beginning in the left parotid. The swelling on the left increased for two days and then subsided. On December 15, there was still swelling of the right gland and a small amount of discharge, but the temperature was normal. The remainder of the recovery was uneventful, and the patient was discharged on December 23.

TABLE 1.—*Age Incidence of Acute Surgical Parotiditis*

	Decade								Total
	1	2	3	4	5	6	7	8	
Cases.....	1	2	15	6	11	9	5	4	56

TABLE 2.—*Incidence of Acute Surgical Parotiditis in Relation to Monthly Admissions\**

	Admissions to Medical Services	Cases of Parotiditis	Admissions to Surgical Services	Cases of Parotiditis
January.....	2,301	6	2,557	0
February.....	2,189	0	2,638	1
March.....	2,489	2	2,599	2
April.....	2,272	2	2,578	1
May.....	2,218	1	2,876	2
June.....	2,503	1	2,814	2
July.....	2,442	3	2,852	1
August.....	2,606	1	2,624	4
September.....	2,595	3	2,689	6
October.....	2,323	1	2,737	3
November.....	2,236	3	2,602	5
December.....	2,308	1	2,239	5

\* In these figures admissions to eye, ear, nose and throat, obstetric and newborn services are omitted.

#### CAUSATIVE FACTORS

*Sex.*—Most of our patients were females. In the medical services there were 12 of each sex, but in the surgical services there were 23 women to 12 men. The disease attacked 17 women following abdominal operations, and of these, 8 had operation for gynecologic conditions (1 in every 400 gynecologic operations).

*Age.*—Our youngest patient was a girl of 9 years (case 9), and our oldest was a man of 87 (case 14). The disease has been reported in infants by Brandt. Table 1 shows the age incidence in our series.

*Month of Occurrence.*—Table 2 shows the incidence of the disease from 1926 to 1939 in relation to services, admissions and months of the year.

Table 3 shows the occurrence by years.

One will note the greater numbers during the last few years. This is partly due to the facts that our hospital population was almost doubled by the addition of Firmin Desloge Hospital and that there has been an increase in the number of patients at St. Mary's Hospital. The large number for 1936, almost one third of all the cases, perhaps shows the causative influence of weather. In that year occurred the hottest summer ever recorded in St. Louis, and 45 per cent of the cases for that year occurred during its three hottest months. The incidence that year was 1 in 647 in contrast with the ordinary incidence of 1 in 2,167. This is in agreement with the observations of Cope.

The admissions for the last half of the year are slightly more than those for the first half, viz., 50.07 per cent, but 64.2 per cent of our cases occurred in the last six months of the year. In the surgical service only 25 per cent of our cases occurred in the first half of the year, while in the same time we received 56.25 per cent of our patients, whereas in the medical service 50 per cent occurred in each half, and the admissions

TABLE 3.—*Occurrence of Acute Surgical Parotiditis by Years*

Year.....	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937	1938
Cases.....	1	0	1	0	2	5	0	0	2	5	6	4	17	8	5

were nearly the same for each half year (13,972 and 14,490). It will be seen that 25 per cent of all the cases occurred in August and September, but November and December contributed the same percentage of cases. And while September was the month most fruitful in the number of cases (16.1 per cent), November was but 1 case behind with 14 per cent of the total. While one is wondering whether after all the weather has anything to do with the condition, we refer again to the hottest year of all, 1936, with its quota of 30.3 per cent of all our cases and to Cope, whose experience was similar to ours.

*Vascular Conditions.*—In 11 patients (cases 3, 6, 7, 9, 13, 14, 15, 17, 18, 23 and 45), 20 per cent of all, advanced arteriovascular renal disease was present in some form, with or without hypertension, nephrosclerosis, uremia or coronary disease. In 2 of these, it is doubtful whether the parotiditis was a causative factor in the outcome.

*Diabetes.*—In 5 patients (cases 2, 5, 22, 29 and 49) who had diabetes, parotiditis developed. Of these, 2 were in coma when they were brought in.

*Condition of Mouth.*—In the reports of 25 of the 56 cases, specific mention is made of the condition of the mouth, and in all, one finds repeated the words "pyorrhea," "caries," "dry," "dirty" or "foul." In

none is mention made that the mouth was in a clean or sanitary condition. Besides this, it should be remembered that another 7 of our cases occurred in those who were being nourished parenterally; in cases in which this type of nourishment is carried out, it is the rule to find the mouth more or less dry. Fenwick called attention to this in 1909 and suggested putting a rubber teat or pebble or a bit of raw meat or horse radish in the mouth to make the saliva flow in order to prevent infection of the gland.

*Respiratory Tract.*—Seven cases of parotiditis appeared in which there were pharyngitis and infection of the respiratory tract, but of these, only one occurred with bronchopneumonia, one during and one after lobar pneumonia—all primary. We call attention to this because the statement has been frequently made (and more frequently copied) that the condition most often follows pneumonia.

*Stone.*—Only 1 case was due to stone in the duct.

*Ear, Nose and Throat.*—The condition has been said not to appear after mouth and throat infections, but 2 of our cases followed tonsillectomy, and 2 followed tooth extractions; 1 followed fracture of the adjacent mandible; 2 of our patients had otitis media, and 1 had a mastoid operation. There were 4 cases in which no cause could be given. This was remarked long ago by Carr and Day and has been confirmed by Nicol, Wagner, Spurling and Stewart, Honigmann and others.

*Peritonitis.*—Parotiditis occurred as a complication with peritonitis in 10 cases, and in these cases, the mortality rate was 60 per cent. Three of these cases followed gynecologic operations.

*Operation.*—Parotiditis is seen a little more often in the combined surgical than in the combined medical services—1 in 1,621 to 1 in 1,779. It is most often found after major abdominal operations—1 in 650 cases.

*Abdominal Operations.*—Twenty-three of our 32 cases occurred in the surgical services, and of these, 8 followed gynecologic operations. Our incidence was 1 in 650 ordinary abdominal operations and 1 in 400 gynecologic abdominal operations. Two cases followed 1,020 operations on the biliary tract (1 in 500); 3 occurred after 300 operations on the stomach (1 in 100); 3 followed 2,640 cases of acute appendicitis (1 in 880), and 2 in 196 operations on the colon (1 in 100). Although we had no cases of infectious parotitis (mumps) complicating any abdominal operations. Addenbrooke and Elder reported cases of this sort. The higher incidence following operations on the colon is in agreement with the findings of Rankin and Palmer.

*Carcinoma.*—Seven of the cases occurred in patients with carcinoma (cases 14, 35, 36, 37, 45, 47 and 54)—2, of the cervix uteri (cases 36 and 37); 2, of the rectosigmoid (cases 45 and 54); 1, of the stomach (case 47); 1, of the urinary bladder with lung metastases (case 14), and

1, of the soft palate (case 35). Only in the last case could the disease have any direct influence on the occurrence of parotiditis. The total number of patients with carcinoma (not including those with sarcoma and other tumors) admitted during the period studied was 3,028, i. e., 3.1 per cent of the total number of admissions. Thus, in cases of cancer, parotiditis occurred once in 432 cases and once in 1,621 of all surgical cases.

The role of anesthesia in the causation of the disease has afforded a topic for speculation. Some, e. g. Wagner and Deaver, blame the anesthetist for traumatizing the gland in his attempts to push the jaw forward. But it has occurred in patients to whom an anesthetic had never been given. We have run across the statement that it has never been recorded after spinal anesthesia.

Twenty-one of our patients were given some kind of anesthetic for some operation preceding the parotiditis, as follows: 12, spinal only, procaine hydrochloride; 2, spinal and ether; 1, spinal and ethylene; 2, spinal and nitrous oxide and ether; 1, avertin with amylene hydrate; 1, morphine-scopolamine-cactin; 1, ether; 1, ethylene and nitrous oxide.

According to these records, then, spinal anesthesia can also claim a following of parotiditis cases, but one can say that the anesthetic was not a causative factor.

#### CLINICAL MANIFESTATIONS

The onset of parotiditis is more often sudden with rapid progression (in 38 of 56 cases) rather than gradual. The first complaint of the patient may be dryness of the mouth or sore throat with pain or soreness at the angle of the jaw (cases 26, 33, 54 and 55). The symptoms may sometimes be so mild before swelling occurs that the patient does not mention them unless questioned; in fact, often the patient is beyond sense of pain before ever the process begins. In a few cases, pain in the parotid region on opening the mouth or on chewing or swallowing or pain in the ear was present before any swelling was visible (cases 20, 38, 39 and 40). Early pain in the ear is possibly due to swelling of the glenoid lobe of the parotid which comes into close relation with the auriculotemporal branch of the third division of the fifth cranial nerve which supplies the parotid and the auricular branches of which supply sensation to the canal, the drum membrane, the tragus and the pinna and to the ear below the meatus externus, so that the inflamed parotid gland gives rise to pain referred along the branches of the nerve to the walls of the external auditory meatus and the tympanic membrane. These branches passing between the cartilaginous and bony parts of the wall of the external auditory canal may be directly compressed when the glenoid lobe of the parotid is inflamed. When the medial portion of the gland lying close to the pharynx is involved, pain and fulness in

the throat or difficulty in swallowing may be present (cases 17, 27, 32, 43 and 56).

Soon after any of these symptoms occur, there is usually a rise in the body temperature, and a swelling is noted just anterior or inferior to the ear at the angle of the jaw.

If the swelling is slight or gradual, there is mild pain, discomfort and soreness in the parotid area (cases 1, 8 and 41), but if the infection is severe and reaction to the inflammation is rapid, within a few hours a marked brawny edematous swelling occurs, frequently carrying the lower part of the ear out from the side of the head. Pain may be intense, and within twenty-four hours, the orbit, the cheek and the neck may be involved, and the overlying skin may or may not be red (cases 3, 6, 7, 9, 17 and 19). As the edema and the swelling increase, the patient may not be able to open the mouth. This was noted particularly in cases 42 and 49. The pain becomes intense, and symptoms of toxemia appear (cases 32, 42 and 49). At first the swelling is limited strictly to the area under which the gland lies. It ends abruptly at the zygoma. In front, its margin can be seen to descend more or less vertically near to the anterior margin of the masseter muscle and the part of the gland below the ear and the angle of the jaw stands out, carrying the lobule of the ear outward and forward and a little upward.

Varying with the intensity and the spread of the inflammation, the fever ranges from 100 to 104 F., and the white blood cell count ranges from 14,000 to 43,000 in 90 per cent of the cases, and only a few fail to show leukocytosis above 9,000. One patient with Still's disease and chronic leukopenia (case 21), showed a count of only 6,700. In 2 cases of mild parotiditis in children the count ranged from 7,000 to 8,500. The patients in cases 3 and 13 had a white blood cell count of 7,500, but here again the course of the parotiditis was only moderately severe.

Parotiditis was present bilaterally in 18 cases—32.1 per cent of all; it was right sided in 20 cases, and left sided in 18 cases. It is not unusual for both glands to enlarge within a few hours of each other (cases 1, 3, 6, 35, 41 and 50). In 1 patient (case 35), the enlargement began simultaneously in both glands, but one gland subsided only to become enlarged and acutely inflamed sixteen days later. In cases 5, 18 and 45, the second gland became involved four to fifteen days after the first.

When the gland on one side becomes swollen rapidly, it is possible that a slight swelling of the gland on the opposite side may be overlooked unless a thorough examination is made, as the swelling in one gland may be slight. The examining finger can palpate the edges of the gland almost as soon as swelling begins.

In 18 cases, the papillae of the parotid ducts were examined within seventy-two hours of the onset of parotiditis. The ducts were found to

be normal in 7 cases, and in the other 11, they showed a raised red edematous orifice with or without pus draining from the papilla. In 6 of the 11 cases, pus was draining from the duct within twenty-four hours of the onset.

Blood cultures were taken in 18 cases once or oftener and in some cases daily, but all cultures were negative except in case 55, in which culture showed *Staph. aureus* from the duct and the gland and *Str. haemolyticus* in the blood stream. This patient recovered.

If the inflammatory process is not interfered with, the swelling may subside without drainage (cases 1, 13, 15 and 41) or drain through the ducts (cases 8 and 48). In other cases, the pus may rupture into the ear or the pharynx or into the mouth (case 5) or form a superficial abscess and rupture through the skin, more often near the mastoid process (cases 5, 37, 47 and 53). When the glenoid lobe is abscessed, the pressure of the pus is directed against the weakest part of the external auditory canal near the bone, resulting in discharge of the pus into the canal (cases 2, 5, 21, 31 and 43). This can be avoided by early operation properly performed. The failure of such inflammation of the gland and the general reaction to subside in case 37 was due to a deep overlooked abscess which ruptured into the ear six days after the capsule of the gland had been opened, but nothing more had been done. Case 42 is another example. It is our belief that this could have been avoided by blunt probing of the gland with the unopened scissors. Petit was explicit in his directions of what to do to avoid this.

Extension into the neck is a frequent and serious complication of parotiditis. In some cases the extension is limited to the spread of the inflammatory edema, and in others there is extension of the acute purulent inflammation into the anterior and posterior triangles of the neck with burrowing of pus along the fascial planes (cases 2, 5, 6, 17, 27, 42 43 and 44). It is dangerous; 50 per cent of such patients died. This did not occur in a single case in which opening was done early and properly.

As the swelling of the gland progresses, the gland may become necrotic or gangrenous before there is an abscess formed (cases 16, 26, 39 and 40). This is due, perhaps, to internal pressure from edema and congestion and the unyielding tough fibrous capsule. The gland has been found black in twenty-four hours (case 39). Even when an abscess does form, fluctuation in some cases may not be palpable owing to the depth from the surface, the tension within the capsule or the swelling of the overlying tissue (case 34); this was attested by Petit and Gross. If an abscess forms in the portion of the gland lying beside the pharynx or in the glenoid lobe, it will not be palpable and may be found only when the gland is incised and probed or may be only inferred from the

subsequent course if pus ruptures into the ear or the pharynx. Such an abscess gives a peculiar quality to the voice not unlike that of peritonsillar abscess.

Necrosis is followed by sloughing, and even the facial nerve may be destroyed with permanent paralysis of the facial muscles on that side (cases 26 and 31). A temporary facial weakness may develop when the swelling is great (cases 27, 42 and 47) and disappear when the edema and the inflammation subside (cases 27 and 47). In 1 case, sloughing of the gland was followed by moderate secondary hemorrhage into the retromandibular space (case 42).

Psychosis may develop (Everke); we have had 2 patients in whom it did (cases 16 and 51). It may be due to fever and toxemia, but it is seen when there is meningeal irritation. In either case, it disappears when drainage is established. In both of our cases, it came on while the patients were convalescing and continued while the patients were in the hospital.

In 1 fatal case (case 31), in which acute mastoiditis and cavernous and lateral sinus thrombosis and general sepsis developed, there was a rupture of the parotid abscess into the external auditory canal with extension of pus back through an old perforation of the tympanic membrane to the middle ear and so to the mastoid. The patient presented symptoms of cerebritis, and an abscess was feared. The autopsy revealed none. Note that at the first and most important operation "a small incision was made." The danger of this variety was stressed by Albert.

During the course of severe parotiditis, acute inflammation of the submaxillary gland on one or both sides developed in 4 patients (cases 4, 16, 40 and 48). Two of these patients required drainage (cases 4 and 48). At one point, the submaxillary gland is separated from the parotid gland only by the fascial capsule, and it has been said that submaxillary gland inflammation may occur by direct extension. We do not find that this has ever been verified.

The patient in case 19 entered with severe pharyngitis. Cultures of the throat showed hemolytic streptococci. When parotiditis developed, the gland was incised, and forty-eight hours later, acute cellulitis and erysipeloid rash appeared. In the following days, the inflammation and the rash extended to the axilla and down the back, but the patient subsequently recovered. Cultures from the gland and the duct showed streptococci.

In 11 cases (cases 6, 16, 19, 26, 30, 38, 39, 40, 45, 46 and 51), the gland was incised within twenty-four hours, and in only 3 (cases 6, 19 and 26) was there any sign of pus, although the glands were unusually acutely inflamed.

To find staphylococcus present in pure culture in the gland of a patient known to have had streptococcic septicemia (case 55) does not

help to sustain the theory that the disease is blood borne. To find it present in the gland alone or to find the gland sterile while at the same time cultures from the duct are positive, pure or mixed, certainly does not help to convince one that all cases arise as ascending infections.

The following case, from the practice of one of us (W. T. C.) may or may not be an example of blood-borne infection:

Dr. ———, 29 years old, was bitten on the finger by an unruly patient. The wound suppurated, and after six weeks, the finger was amputated. The pus from the finger showed gram-positive fusiform bacilli and staphylococcus, and the discharge was foul smelling. One week after the amputation, the patient was suddenly stricken with what looked like an attack of acute cholecystitis. This was so severe that he was operated on within twenty-four hours. There was gangrene of the fundus of the gallbladder, and the fundus was tightly distended with brownish seropurulent material which smelled like the discharge from the finger. Exactly the same organisms grew from cultures of this as from those of the finger. Some days later, parotiditis suddenly developed; this was incised, and brownish seropurulent material with the same foul odor as that of the other discharges escaped. This also showed the fusiform bacilli and the cocci. Cellulitis of the neck developed, and subcutaneous metastatic abscesses were later widespread. From the first of the abscesses opened, the same organisms were recovered. The patient finally recovered and at the time of writing is still well.

Carr suggested that the disease might originate in the same way as the similar condition affecting the abdominal parotid, i. e., the pancreas. But are all agreed as to the origin of that?

#### TREATMENT

Treatment must be directed against the cause if the morbidity rate is to be appreciably reduced. Since the chief contributing factors of parotiditis seem to be poor oral and dental hygiene, dryness of the mouth from oral starvation, dehydration and decreased salivary secretion and general lowered resistance either from age with advanced vascular damage, nephritis, diabetes and respiratory infection or from acute inflammatory lesions with toxemia, such as peritonitis, prophylactic measures to prevent or to ameliorate these should help to reduce the incidence and to lessen the severity of the disease.

Fenwick, Charlton and others suggested care of the mouth and teeth preoperatively and the use of oral fluids, lemon and lemon candy stick. Dorrance advised gum chewing and like methods to maintain adequate parotid secretion. Many have used these methods, and we use them routinely. Morphine has been considered as inhibiting the secretions of the gland, and the use of atropine with it before operation has some effect in keeping the mouth temporarily dry, but there is no evidence to show that these have any relation to the occurrence of parotiditis.

Rolleston and Oliver thoroughly demonstrated that water by mouth during treatment for peptic ulcer reduces the incidence of parotiditis.



Prophylactic measures such as those hereinafter described should be instituted:

1. Dental caries, pyorrhea and pharyngitis should be corrected as soon as possible after entry. If the patient has any operative condition, unless operation is urgent, carrying out the procedure should be deferred until oral and dental hygiene are satisfactory and the upper respiratory area is free from infection.

2. Adequate fluid intake by mouth should be maintained when possible, and when not, at least cracked ice should be allowed, and the mouth and the throat should be flushed with sour-tasting fluids at least once every two hours.

3. The general resistance and the vitality of the patient should be improved by the intravenous administration of blood, serums, water, salt and dextrose.

4. The salivary flow should be encouraged by the use of chewing gum, lemon or orange juice and candy.

5. Proper nursing care is particularly important for those patients who are seriously ill and unable to care for their mouths, throats and teeth and who must be helped with their food, fluids and gargles. In elderly persons there is the tendency to sleep with the mouth open, and other people are mouth breathers. These particularly need care for oral dryness and foul mouth. Keep the mouth closed by a chin strap bandage, unless there is nasal obstruction. Frequent gargles with solution of sodium perborate (3 to 5 per cent in water) or other cleansing oral washes should be used.

If parotiditis supervenes in spite of all prophylactic measures, we continue to give attention to the condition of the mouth, but, in addition, the local condition is treated.

During the first twenty-four hours, local application of cold is used in all cases during the first day at least. It has been the custom of one of us (W. T. C.) to apply cold constantly during the first twenty-four hours and if the condition has improved or is no worse, to continue it. If the condition does not improve, hot packs or poultices of linseed meal made with 25 per cent glycerin in water are applied and changed frequently for another twenty-four hours. If improvement is now present, one may wait, but if not, the gland is uncovered right away, and then the hot applications are continued. We do not mean merely to give the patient a hot water bag or an electric pad and tell him to apply it. Better results are obtained with generous hot wet packs or poultices renewed once an hour at least. In 1939, one of us (E. R. G.) treated a patient outside the University's hospitals, using 120 grains (7.76 Gm.) of sulfanilamide for the first twenty-four hours and 80 grains (5.18 Gm.) for each of the following days. Although the onset

was abrupt and the gland swelling extensive, in the first twenty-four hours, the inflammation did not progress, and the patient recovered without surgical intervention. Since 1939, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), which is considered most effective against staphylococcus, has come into use, but no patient whose case is here reported received it. Since the offending organism is usually staphylococcus, sulfanilamide derivatives may completely alter the treatment, the prognosis and the mortality rate of parotiditis. At present, surely, early and adequately large doses of sulfathiazole are indicated.

Many have advised waiting until pus forms, determinable by fluctuation or aspiration, and then opening. Some have advised massage and aspiration of the duct. Others give iodine and potassium iodide (e. g., Morison). More recently roentgen and radium radiation have had their advocates. In our series, roentgen radiation was used on only 2 cases (cases 48 and 50), and radium was not used at all. Bowing and Fricke presented figures to show that treatment with radium gives a better prognosis—a 23 per cent mortality rate.

Our study seems to indicate that early operation gives better results than late operation or expectant treatment. We had 24 patients operated on under seventy-two hours with a mortality rate of 29.1 per cent. There were 17 operated on after seventy-two hours with a mortality rate of 41 per cent. There were 15 on whom no operation was performed; 8 of these died—a mortality rate of 53.3 per cent. Early operation is probably avoided because of the physician's belief that no operation should be done before suppuration is demonstrable.

We made cultures from 16 patients operated on within forty-eight hours (there was no fluctuation in any of these). The cultures failed to yield a growth in only 3 cases, and in 1 of the 3 (case 40) the gland was gangrenous. Gangrene was present in cases 16, 39, 40 and 55 within twenty-four hours. Among 24 patients operated on within seventy-two hours pus was present in 8 only—33.3 per cent. And among these, although pus was said to be present, in not one had fluctuation or abscess developed. "The pus infiltrates into the tissue," wrote Cruveilhier and others. We feel, therefore, that to delay uncovering the gland is to increase the hazard. To do less than uncover the gland in the early hours, we feel cannot do much good. Simple incision before abscess has formed will probably be ineffective. After it has been uncovered, the hot moist (hypertonic) application should be continued.

The fear of scarring is another factor which is likely to defer operation. Properly placed incisions leave a scarcely noticeable scar.

We have run across the following dictum in the works of Paget and of some others: "*Parotidites omnes, ante maturitatem semper aperiendae.*" We have not found who first said it, but a thesis by Baron, in 1744, disputed the axiom. (The same thesis, word for word,

was accepted from another candidate twenty-four years later.) So it seems to have had the weight of authority. We think Baron was right, that opening should not be done in all cases before maturity but it seems to us that those which are plainly no better after forty-eight hours' treatment should at once be uncovered. Of course, when the disease occurs in a manifestly dying patient, any operation is contraindicated.

We have spoken of uncovering the gland. A vertical skin incision is made in front of the ear connecting with an oblique incision below and behind the ear. If the vertical incision is kept close to the ear and if one cuts only deep enough to incise the capsule, there is no danger of cutting either a large vessel or the facial nerve. With the blunt scissors, the capsule is separated from the gland forward to its anterior border, and then the capsule only is incised with a transverse incision just below the zygoma and another just above the angle of the jaw. The unopened scissors is then thrust into the gland in various places and opened as withdrawn. The oblique incision below follows the natural crease or groove in the skin and reaches well forward, incising the gland capsule and uncovering the gland from its most posterior tip behind the ear to its most anterior tip below the angle of the jaw. The edges of the incised capsule are now reflected (both the upper and the lower surfaces) until the whole gland has been exposed to view. A bit of rubber is placed between gland and capsule everywhere, and the wound is left wide open and hot hypertonic packs with 25 per cent glycerin are applied and renewed *pro re nata*.

#### PROGNOSIS

In many cases the prognosis must be that of the accompanying disease. Patients who are moribund before parotiditis begins will probably die sooner on account of it. Others, not fatally ill, may soon become so because of it.

So long as the infection remains confined to the gland, the danger is not great, but once the capsule is broken and the infection invades the neck, the prognosis becomes bad—50 per cent of the patients with this type died. Or if the base of the skull becomes bathed in pus, meningitis with death is likely to ensue; this was the observation of Orthner and was exemplified in our case 31.

In the 56 cases here recorded, 37 patients recovered, and 19 died. The patient in case 48 is considered as recovered since he had fully recovered from parotiditis before the last operation was undertaken. Thus, there were 19 deaths in 56 cases—a general mortality rate of 33.9 per cent. The mortality rate is highest of all among those who have the cardiovascular-renal changes incident to or causing hypertension or occurring as a consequence of old age or constitutional disease. These constituted one fifth of our patients, and their mortality rate was

81.8 per cent. Peritonitis from almost any cause has a poor prognosis. Among the cases of parotiditis occurring in the course of this disease there was a death rate of 60 per cent. There were 23 cases which followed abdominal operations, and 9 of the patients died (6 with associated general peritonitis)—a mortality rate of 38.1 per cent (the general mortality rate, 33.9 per cent). Altogether there were 32 cases which followed operative conditions, and 10 of the patients died—a mortality rate of 31.2 per cent.

It has been said that gangrene of the gland always results in death. This in our series was not true. There were 10 patients with gangrenous

TABLE 4.—*Mortality Rates in Published Reports*

Author	Mortality Rate, per Cent	Cases Reported
Morely .....	25.2	57
Charlton.....	30.7	13
Bowing and Fricke.....	22.8	184
Spurling and Stewart.....	36	22
Blair and Padgett.....	42.5	35

TABLE 5.—*Mortality Rate in Relation to Decade of Life*

Decade	Onses	Deaths
First.....	1	0
Second.....	2	1
Third.....	15	3
Fourth.....	6	2
Fifth.....	11	2
Sixth.....	9	3
Seventh.....	5	1
Eighth.....	4	4
Ninth.....	3	3

glands (cases 5, 16, 26, 27, 39, 40, 47, 50, 52 and 55) and of these only 3 died (cases 39, 40 and 52)—a mortality rate of 33.3 per cent (general mortality rate, 33.9 per cent).

Again, we have read that "bilateral cases are likely to end fatally." In this series there were 18 cases of bilateral parotiditis (cases 1, 3, 4, 5, 6, 9, 16, 18, 25, 35, 37, 41, 43, 45, 46, 48, 50 and 56), 32.1 per cent of all. Thirteen of the patients recovered—a mortality rate of 27.7 per cent (general mortality rate, 33.9 per cent).

There were 38 cases of unilateral parotiditis, and 14 of the patients died—a mortality rate of 36.8 per cent (general mortality rate, 33.9 per cent).

Table 4 shows the mortality rate in some published papers in which more than 10 cases were reported.

Table 5 shows the mortality rate in relation to age by decades.

## CONCLUSIONS

Any acute parotiditis other than mumps is a surgical disease from beginning to end. This is true whether the disease occurs per se or as a complication or sequel of some other disease.

The incidence in ordinary hospitals in the St. Louis area is about 1 in 2,000 cases.

The disease occurs with almost equal frequency among the medical and surgical patients, but of the cases occurring in surgical patients, about 85 per cent follow major surgical operations.

Parotiditis occurs most often in those with dry and at the same time poorly cleansed mouths (tongues and teeth).

The most frequent bacterial cause is staphylococcus (aureus and albus).

Early treatment with adequately large doses of sulfanilamide derivatives is indicated. At present, sulfathiazole is probably best.

The mortality rate is lower among those cases in which there are surgical indications if incision and uncovering of the gland are done early and properly.

Simple incision is of use only when frank abscess exists.

While our experience with treatment by radiation is too small to be of value, nevertheless, the published reports of those who have had large experience with this treatment, particularly with radium, seem to indicate that it is a valuable form of treatment.

The safest form of operative treatment consists in uncovering the whole gland and making multiple openings in its substance with a blunt instrument.

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# DUODENAL BULB ACIDITY UNDER FASTING CONDITIONS IN PATIENTS WITH DUODENAL ULCER

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From the standpoint of the frequency of clinical occurrence, the most susceptible of the areas subject to the ulcerating influences of the acid gastric juice is the first part of the duodenum. Yet, there is little information available regarding the acidity in this important ulcer-bearing region in marked contrast with the extensive studies made on acidity in the stomach.

The study to be reported was undertaken to obtain data on acidity in the duodenal bulb under fasting conditions in patients with an ulcer at that site for comparison with comparable data obtained during digestion in the same subjects<sup>1</sup> and with data from fasting normal subjects.<sup>2</sup> The results will widen the knowledge of the trend of events in the duodenal bulb and should enable further appraisal of the relation between the acidity in this area and that simultaneously observed in the stomach. The comparisons, we hope, will shed more light on the effect of ulceration on the reaction and the neutralizing ability of the contents of the duodenal bulb and will afford better criteria with which to evaluate the acid factor in duodenal ulcer.

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1. Berk, J. E.; Rehfuß, M. E., and Thomas, J. E.: *The Effect of Ulcer on the Acidity and Neutralizing Ability of the Duodenal Bulb*, Arch. Int. Med., to be published.

2. Berk, J. E.; Rehfuß, M. E., and Thomas, J. E.: *Duodenal Bulb ("Ulcer-Bearing Area") Acidity in Fasting Normal People*, J. Lab. & Clin. Med., to be published.

## MATERIAL

The 26 subjects utilized for the purpose of this study were selected at random from the wards and the outpatient gastrointestinal clinic of the Jefferson Medical College Hospital. All presented symptoms suggestive of an active ulcer; some had a history of episodes of bleeding, and all showed an active nonobstructive duodenal ulcer without any recognizable lesion in the stomach when examined roentgenologically. A few were examined additionally with a gastroscope and showed a normal gastric mucosa.

Experiments were considered technically satisfactory in 23 of the subjects (17 males and 6 females), and only the results from these were accepted. The age of the entire group ranged from 21 to 59 years with an average of 41.7 years. The male subjects ranged in age from 21 to 57 years with an average of 40.7 years; the female subjects, from 21 to 59 years of age with an average of 44.2 years.

## METHOD

Each subject was studied in the morning before breakfast and after a fast of at least twelve hours. A specially constructed tube with a double lumen was employed, and a method was followed which furnished more or less fluoroscopic control as well as roentgen proof of the position of the tube.<sup>3</sup> All the patients had experienced varying numbers of previous gastric analyses, and the swallowing of a tube was for them an easy and accustomed procedure. For the same reason, they were able to take a meal with the tube in place without undue difficulty and without nausea or vomiting. We were able, in a number of patients, to manipulate the tube from the stomach into the duodenum with the aid of fluoroscopic guidance. The remaining patients were placed at rest on their right sides and instructed slowly to swallow the tube over a period of half an hour; during this time they were left alone in a quiet darkened room. In some instances the tube had to be withdrawn at the end of this time and reswallowed. The experiment was discontinued or discarded in all cases in which there was occasioned any distress, nausea or vomiting.

After the desired position of the tube was satisfactorily achieved and fluoroscopically confirmed, specimens were withdrawn simultaneously from the pars pylorica and the duodenal bulb at ten minute intervals for half an hour. The  $pH$  of each sample was determined without delay through the use of a Leeds-Northrup  $pH$  indicator, which employs a glass electrode. The free and the total acidity of each specimen were titrimetrically estimated after filtration, Töpfer's reagent and phenolphthalein being used as the respective color indicators. On each duodenal sample, in addition, there was determined what we called the "excess neutralizing ability." This consisted of the amount of tenth-normal hydrochloric acid needed to bring about a positive colorimetric reaction for free acid.<sup>4</sup>

Of the 74 experiments which were made, 63 were accepted as satisfactory from the technical viewpoint. These comprised 1,369 separate determinations, consisting of 381 estimations of  $pH$ , 398 determinations of free acid, 398 determinations of total acidity and 192 estimations of excess neutralizing ability of the duodenal contents.

3. Berk, J. E.; Reh fuss, M. E., and Thomas, J. E.: A Method for the Simultaneous Aspiration of the Contents of the Stomach and First Part of the Duodenum, J. A. M. A. 119:259 (May 16) 1942.

4. Berk, J. E.; Thomas, J. E., and Reh fuss, M. E.: Limitations in the Use of Color Indicators in Gastric Analysis, Am. J. Digest. Dis. 9:106, 1942.

## RESULTS

*Acidity in  $p_H$  Units (fig. 1).*—Stomach: The average gastric  $p_H$  for the entire observation period was 1.62, indicating a much greater acid concentration than did the corresponding average  $p_H$  in fasting normal subjects ( $p_H$ , 3.51).<sup>2</sup> This was seen further in the fact that all the samples in these fasting patients with ulcer had a  $p_H$  below the critical level of 3.5 which we had adopted as indicating the presence of free acid,<sup>4</sup>

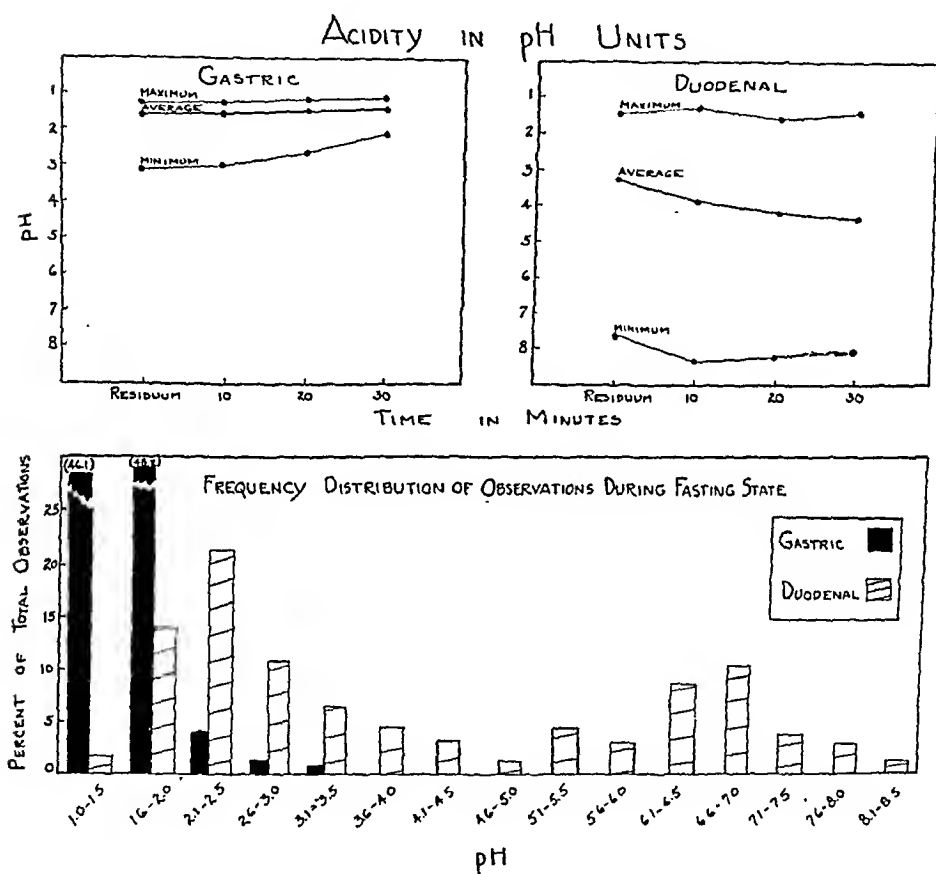


Fig. 1.—Acidity in  $p_H$  units of samples collected simultaneously from just above and just below the pylorus in fasting patients with duodenal ulcer.

whereas, in fasting normal subjects previously examined, almost one third of all the gastric samples had a  $p_H$  above 3.5. When these data are compared with similar data from patients with ulcer fed an Ewald meal,<sup>1</sup> the average  $p_H$  values are seen to be approximately equal, and the range of the individual values practically coincide.

Duodenum: The over-all average duodenal acidity in terms of  $p_H$  was 3.96, which was much greater than that previously found in fasting normal persons (5.60). Furthermore, over half (55.8 per cent) of all

the samples from fasting patients with ulcer had a  $p_H$  above 3.5 (positive for free acid) compared with only one fourth (26 per cent) in fasting normal subjects. Despite the increase in over-all acidity, there was a consistent difference in  $p_H$  between specimens simultaneously withdrawn from areas just above and just below the pylorus, which averaged 2.34  $p_H$  units. This difference exceeded that in fasting normal subjects (2.09  $p_H$  units). Of all the average duodenal  $p_H$  values, only that for the first sample (fasting duodenal residuum) was less than the critical value for free acid.

The line representing the plotted values for average duodenal  $p_H$  showed a trend toward decreasing acid concentrations with each aspiration. This line, just as in normal subjects, was of an entirely different configuration than the corresponding one for average gastric  $p_H$ .

Fluctuation in the reaction of the contents of the first part of the duodenum was more pronounced in these patients than in normal subjects, although the contrast between the two groups in this respect was not so prominent under fasting conditions as during digestion.<sup>1</sup>

*Free Acid* (fig. 2).—Stomach: Gastric free acid averaged 31 clinical units. This and also the range of distribution of the individual values exceeded those in fasting normal people (average 15 clinical units). In both respects the findings closely resembled those in patients with ulcer after an Ewald meal.

It is interesting to note the difference in pattern of the graphic curves of average gastric free acid and average duodenal  $p_H$  (fig. 1).

Duodenum: Free acid as determined colorimetrically was present in the contents of the first part of the duodenum in 44.4 per cent of the samples. This is more than four times the frequency observed in fasting normal persons. The percentages are less than the corresponding figures based on  $p_H$  values (fig. 1) owing to a certain number of false negative readings resultant from our method of filtration and dilution of the samples preparatory to colorimetric titration.<sup>4</sup> Since our end point with Töpfer's reagent was about  $p_H$  3.5, we assumed that all samples of which the  $p_H$  in the unfiltered, undiluted state was 3.5 or less contained free acid.

Colorimetrically, 60.8 per cent, and electrometrically, 78.2 per cent, of all the patients with ulcer used in this study had free acid in the contents of the duodenal bulb as compared with 22.7 per cent, colorimetrically, and 40.9 per cent, electrometrically, of fasting normal subjects previously studied. Free acid, when present, tended to persist over a longer period than in normal subjects. For example, of the fasting patients with ulcer, 8.7 per cent, colorimetrically, and 39.1 per

cent, electrometrically, showed free acid in every one of the four observations, whereas colorimetrically, none, and electrometrically, only 1 normal subject showed this.

Despite a fairly close similarity in average values and in range of values for gastric free acid, fewer fasting patients with ulcer showed free acid in the contents of the duodenal bulb than did the same patients after an Ewald meal, and fewer duodenal samples were positive for free acid under fasting conditions than during the digestive phase.

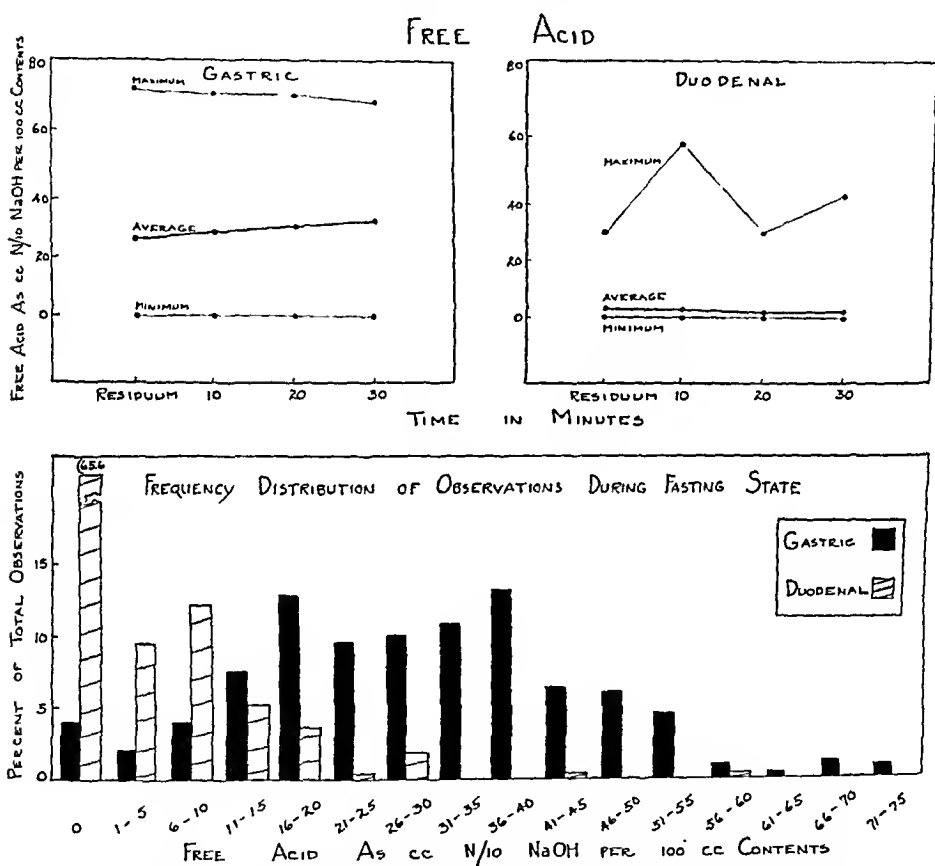


Fig. 2.—Free acid as determined on samples collected simultaneously from just above and just below the pylorus in fasting patients with duodenal ulcer.

**Total Acidity** (fig. 3).—Stomach: Total acidity in the stomach averaged 58 clinical units, which exceeded the corresponding value found in fasting normal subjects (38 clinical units). However, both the average value and the range of the individual values were less than those observed after a meal in the patients with ulcer.

The line representing the plotted values for average gastric total acidity showed rather prominently the trend toward increased acidity

values with each successive determination; this was seen also in the case of average gastric  $p_H$  and free acid. There was a divergence between this line and those representing average duodenal  $p_H$  (fig. 1) and average duodenal total acidity (fig. 3), respectively.

Duodenum: The average total acidity in the duodenal samples was 24 clinical units; this also was greater than that found in fasting normal subjects (18 clinical units). However, these values indicated a reduction

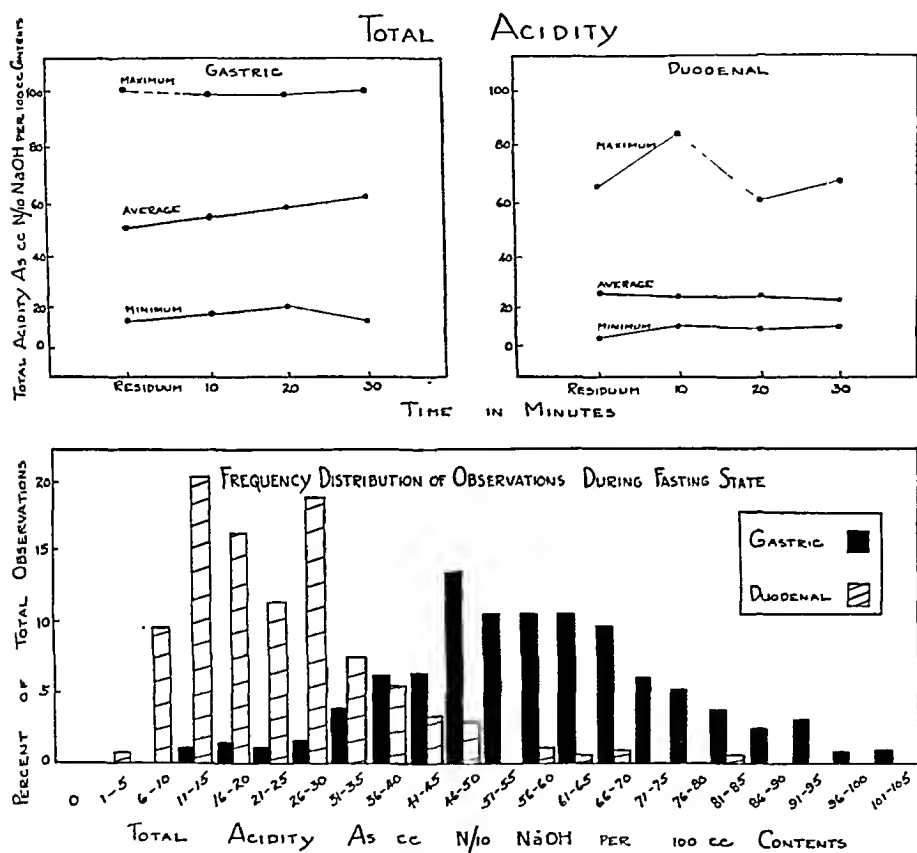


Fig. 3.—Total acidity of samples collected simultaneously from just above and just below the pylorus in fasting patients with duodenal ulcer.

from the average gastric total acidity of 59 per cent in the patients with ulcer as compared with 53 per cent in normal subjects.

*Excess Neutralizing Ability of the Duodenal Contents* (fig. 4).—“Excess neutralizing ability of the duodenal contents” has been defined as a measure of reserve capacity which the contents of the duodenal bulb possess to neutralize, buffer and dilute the gastric secretions above that necessary to offset free acid content.<sup>4</sup>

The average excess neutralizing ability of the duodenal bulb contents was 11 clinical units, which is less than that found in either fasting

normal persons (17 clinical units) or patients with ulcer after an Ewald meal (14 clinical units). Of all the duodenal samples, 37.5 per cent failed to show any excess neutralizing ability as compared with 14.5 per cent of those from fasting normal subjects and 43.1 per cent of those from patients with ulcer fed an Ewald meal. The range of the individual values was slightly less than in fasting normal subjects and distinctly less than in patients with ulcer after an Ewald meal.

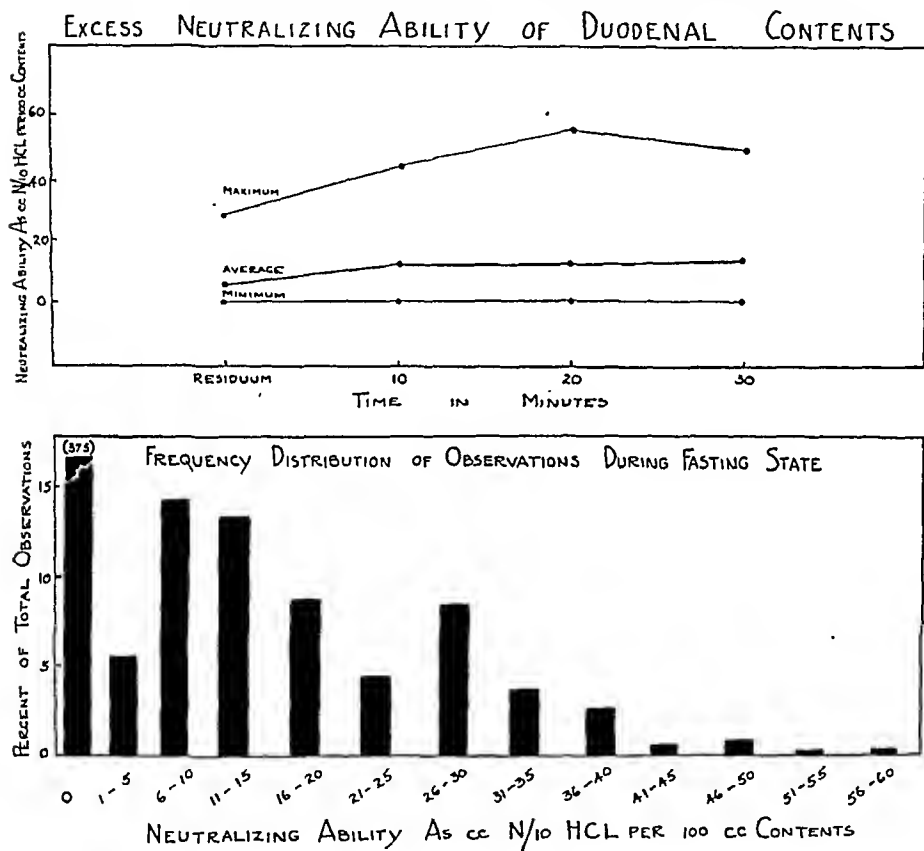


Fig. 4.—Excess neutralizing ability of the contents of the first part of the duodenum in fasting patients with duodenal ulcer.

#### COMMENT

Whether or not the stomach has a true fasting secretion is still controverted.<sup>5</sup> Aside from the local and constitutional changes in

5. (a) Babkin, B. P., in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues: Does the Stomach Secrete Gastric Juice Continuously? New York, International Press, 1932, vol. 1, p. 113. (b) Bloomfield, A. L.; Chen, C. K., and French, L. R.: Basal Gastric Secretion as a Clinical Test of Gastric Function with Special Reference to Peptic

patients with ulcer, which are believed to induce a more or less continual excitation of gastric secretion, other stimuli, normal and abnormal, sufficient to affect the secretory activity of the stomach<sup>5a</sup> probably existed in our patients despite our efforts to minimize them and to produce a true state of stomach rest. Furthermore, a fair degree of experimental error exists in our method of study so that we could not be certain, in spite of all our precautions, that the material supposedly aspirated from the pars pylorica and the duodenal bulb was actually obtained from those regions in every instance. We make no claim, therefore, that the quantitative values we obtained necessarily represent the acidity values which are characteristic for these areas in all patients with duodenal ulcer under fasting conditions. We believe, however, that there are no serious objections which can be raised against their use for purposes of comparison with corresponding values obtained under similar experimental conditions in fasting normal subjects or in patients with ulcer fed an Ewald meal.

Our observations confirm the findings of other investigators<sup>6</sup> to the effect that fasting values of gastric acidity are higher in patients with duodenal ulcer than in normal people. It is probably highly significant that in terms of average values, gastric acidity in fasting patients with ulcer approximates those in the same patients following an Ewald meal; in individual instances, the values during fasting are even greater. We made no attempt to measure the volume of material obtained, but it was our impression that, in general, the patients with ulcer have larger amounts of fasting secretions, both gastric and duodenal.

The contents of the first part of the duodenum are not only more acid in fasting patients with duodenal ulcer than in fasting normal

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Ulcer, *J. Clin. Investigation* **19**:863, 1940. (c) Carlson, A. J.: The Secretion of Gastric Juice in Health and Disease, *Physiol. Rev.* **3**:1, 1923. (d) Pavlov, I. P.: The Work of the Digestive Glands, Philadelphia, J. B. Lippincott Company, 1910. (e) Pollard, W. S., and Bloomfield, A. L.: Basal Gastric Secretion in Man, *Bull. Johns Hopkins Hosp.* **49**:302, 1931. (f) Rehfuß, M. E.; Bergeim, O., and Hawk, P. B.: Gastro-Intestinal Studies: I. The Question of the Residuum Found in the Empty Stomach, *J. A. M. A.* **63**:11 (July 4) 1914. (g) Rehfuß, M. E.: The Diagnosis and Treatment of Diseases of the Stomach, Philadelphia, W. B. Saunders Company, 1927.

6. Bloomfield, A. L.: The Problem of Gastric Hyperacidity, *Am. J. Digest. Dis.* **6**:700, 1939. Bockus, H. L.; Glassmire, C., and Bank, J.: Fractional Gastric Analysis in Two Hundred Cases of Duodenal Ulcer, *Am. J. Surg.* **12**:6, 1931. Vanzant, F. R.; Osterberg, A. E.; Alvarez, W. C., and Rivers, A. B.: Studies of Gastric Pepsin: II. Secretion of Pepsin in Cases of Duodenal Ulcer and Pseudo-Ulcer, *J. Clin. Investigation* **12**:557, 1933. Winkelstein, A.: One Hundred and Sixty-Nine Studies in Gastric Secretion During the Night, *Am. J. Digest. Dis. & Nutrition* **1**:778, 1935. Bloomfield, Chen and French.<sup>5b</sup> Rehfuß.<sup>5c</sup>



subjects, but duodenal neutralizing capacity is overcome for longer periods. The ability of the contents of the duodenal bulb in fasting patients with ulcer to neutralize, buffer and dilute the gastric secretions is still in evidence, even though inadequate to maintain constantly a normal reaction in the duodenum in the presence of the increased gastric acidity. It is, however, such that in fasting patients with ulcer the increase over the normal in duodenal acidity falls far short of proportionately paralleling that in the stomach; the average duodenal acidity in terms of  $p_H$  represents an increase over normal values of only 29.2 per cent, whereas the average gastric acidity is increased by 53.8 per cent over the normal.

The increased acidity in the duodenal cap of fasting patients with ulcer does not appear to be accounted for alone by the higher values for gastric acidity which they display. When the average acidity in terms of  $p_H$  in the stomach and the duodenum in our group of patients with ulcer was compared with acid values of a group of 6 normal subjects whose gastric acid values were comparable to those of patients with ulcer and who were studied in the same manner, it was found that despite similar average gastric  $p_H$  values in both groups ( $p_H$  1.62 and 1.63, respectively), the average duodenal  $p_H$  in normal people was higher (patients with ulcer, 3.96; normal subjects, 4.24). The difference, it is true, was not great, yet a similar but somewhat wider deviation from the normal in this respect was noted by us in a group of patients with ulcer when compared after receiving an Ewald meal with normal subjects whose gastric acidity was likewise high.<sup>1</sup> While by no means conclusive, such findings strongly suggested that in patients with duodenal ulcer there is inadequate neutralization of the gastric acid in the duodenal bulb as well as gastric hypersecretion. The more pronounced fluctuation in the reaction of the contents of the first part of the duodenum of fasting patients with ulcer may represent another expression of a defective duodenal neutralizing mechanism. Some derangement in duodenal neutralization has been suggested before as one of the basic disturbances in duodenal ulcer,<sup>7</sup> and our results support this impression.

The neutralizing capacity of the contents of the duodenal cap in patients with ulcer under fasting conditions appears to be as good or better than during digestion of an Ewald meal. Under fasting conditions, in spite of a fairly close similarity in gastric acidity during

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7. Kearney, R. W.; Comfort, M. W., and Osterberg, A. E.: Hydrogen Ion Concentration of the Duodenal Contents Under Fasting Conditions in Normal Persons and in Patients with Duodenal Ulcer: A Comparative Study, *J. Clin. Investigation* 20:221, 1941. Morton, C. B.: (a) Observations on Peptic Ulcer: VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analysis, *Am. J. M. Sc.* 177:65, 1929; (b) Observations on Peptic Ulcer, *South. Surgeon* 3:316, 1934.

fasting and after a meal, fewer patients have free acid in the contents of their duodenal bulbs; fewer duodenal samples contain free acid, and the average excess neutralizing ability of the duodenal bulb contents is less. These may be indications of a more efficient regulatory mechanism under fasting conditions. On the other hand, they may indicate merely that a greater strain is thrown on an inadequate mechanism during digestion.

Of great interest was the lack of sharp parallelism between the several indexes of gastric acidity on the one hand and the duodenal  $p_H$  as well as the other corresponding indexes of duodenal acidity on the other. On the strength of the discrepancies apparent in the several graphic curves, it seems well advised to warn that none of the customary measures of gastric acidity can be taken as reliable indexes of the behavior of the hydrogen ion concentration in the duodenal bulb over the same period.

#### SUMMARY AND CONCLUSIONS

Under fasting conditions, the contents of the first part of the duodenum in patients with duodenal ulcer are more acid than in normal subjects. In fasting patients with ulcer, they have an average  $p_H$  of about 3.9.

During fasting, free acid is found more often in the contents of the first part of the duodenum in patients with an ulcer in that situation than it is in normal subjects. Free acid when present in the duodenal bulb contents in fasting patients with ulcer tends to persist for longer periods than in normal persons.

The ability of the contents of the duodenal bulb in fasting patients with ulcer to neutralize, buffer and dilute the gastric secretions is impaired but not wholly lost. The impairment is probably largely due to gastric hypersecretion, but a defective neutralizing capacity in the duodenal bulb seems to be present as well.

The neutralizing capacity of the contents of the duodenal cap in patients with ulcer under fasting conditions appears to be as good as or better than during digestion of an Ewald meal.

There is no constant parallelism in the behavior of the simultaneously determined gastric and duodenal bulb acidity.

Dr. B. B. Vincent Lyon permitted the use of the patients and facilities of the gastrointestinal clinic, and Drs. Melvin Dillman and Karl Kornblum performed the roentgen studies on each subject.

1025 Walnut Street.

# CAPILLARY PERMEABILITY AND INFLAMMATION IN THE SKIN OF RABBITS

## EXPERIMENTAL STUDIES FOLLOWING SECTIONING OF THE SPINAL CORD

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MEMPHIS, TENN.

Lauer<sup>1</sup> recently stated that the intensity of the inflammatory reaction was diminished after sectioning the spinal cord. The reactions, however, were similar above and below the injured segment of the cord. The similarity of these two inflammatory reactions, therefore, would make it impossible to ascribe this diminished reaction either to the separation of the organ from its nervous centers or to the loss of pain sensations.

Capillary permeability and inflammation in the skin of the rabbit have been studied by one of us (R. H. R.<sup>2</sup>). The technic used in these studies consisted of applying xylene to the shaven skin of the rabbit at intervals preceding the intravenous injection of trypan blue. A definite pattern of localization of dye occurred in the xylene-treated areas. This dye localized first and in the largest quantity in the area where xylene was applied the shortest time before the dye was injected. The localization and the concentration of dye in the xylene-treated areas of skin occurred inversely with the interval between the application of the irritant and the injection of the dye. If the irritant was placed on a local area of skin thirty minutes before the dye was injected, a smaller amount of dye localized and concentrated in the area than occurred in an area where xylene was applied immediately before the dye was

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This study was aided by grants from the John and Mary Markle Foundation and the University of Tennessee.

1. Lauer, N.: Influence of the Central Nervous System on Inflammatory Reactions: IV. Influence of Cord Section on Non-Specific Inflammation, *J. Med. Ukraine* 9:29-38, 1939; abstracted, *Brit. Chem. & Physiol. A.* 3:113, 1940.

2. Rigdon, R. H.: Capillary Permeability in Areas of Inflammation Produced by Xylene, *Arch. Surg.* 41:101 (July) 1940.

injected. When the irritant was applied three hours or longer before the dye was injected, no more dye localized and concentrated in the xylene-treated areas of skin than in the untreated skin.

The problem of capillary permeability and inflammation has been studied also by intradermally injecting various irritants, such as aleuronat, staphylococci and staphylococcus toxin and thereafter removing the tissues at various intervals for microscopic study. Variations in the normal pattern of the localization of trypan blue and an inhibition in the localization of leukocytes induced by the application of xylene have been found; first, in animals narcotized by ether and alcohol<sup>3</sup>; second, in those given large doses of epinephrine<sup>4</sup>; third, in rabbits sick as a result of a severe staphylococcus septicemia,<sup>5</sup> and fourth, in animals suffering from a profound lowering of the blood pressure following hemorrhage.<sup>6</sup>

Since the tone of the blood vessels is affected to a definite degree by sympathetic impulses transmitted through the spinal cord and since the vascular reaction is of such importance in the mechanism of inflammation, it was decided to study this reaction in the skin of rabbits following the sectioning of the spinal cord.

#### MATERIALS AND METHODS

Adult rabbits were used. The skin over the abdomen and along the lateral portion of the thighs was carefully shaved twenty-four hours or longer before the experiments were begun. Xylene was carefully applied with a cotton applicator to local areas of the skin preceding the intravenous injection of 10 cc. of a 0.2 per cent solution of trypan blue. The time of the appearance of the dye and the intensity of the staining of the areas of skin were observed. In some of the experiments 0.2 cc. of a saline suspension of staphylococci and an equal quantity of a 1 per cent suspension of aleuronat were injected intradermally. The xylene-treated areas of skin and those into which aleuronat and staphylococci were injected were removed after varying intervals, and they were placed immediately into a 4 per cent solution of formaldehyde. Paraffin sections were prepared and stained with hematoxylin and eosin.

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3. Cressman, R. D., and Rigdon, R. H.: Capillary Permeability and Inflammation, in Narcotized Rabbits, *Arch. Surg.* **39**:586 (Oct.) 1939.

4. Rigdon, R. H.: A Study of Capillary Permeability and Inflammation in Skin of Rabbits Given Adrenalin, *Surgery* **8**:839 (Nov.) 1940.

5. Rigdon, R. H.: An Experimental Study of Capillary Permeability and Inflammation in Rabbits with Staphylococcus Septicemia, *Arch. Surg.* **44**:129 (Jan.) 1942.

6. Rigdon, R. H.; Miles, R. M., and Bland, R. P.: The Effect of Low Blood Pressure upon Capillary Permeability and Inflammation in the Skin of the Rabbit, *Surgery*, to be published.

The spinal cord was sectioned under local anesthesia induced with procaine hydrochloride. In some of the rabbits, the cord was cut at the seventh cervical segment and in others at the level of the fourth lumbar segment. A cannula was put into the carotid artery. The blood pressure was recorded at intervals with a mercury manometer.

The white blood cells were counted in some of these rabbits. Blood was removed from the ear. A standard technic was used for counting these cells.

#### EXPERIMENTAL

The cervical portion of the spinal cord was sectioned in 9 rabbits. The blood pressure was recorded in some of these both before and after the cord was cut. In some of the rabbits, the observations were made only following the sectioning of the cord. The normal pressure in these rabbits varied between 100 and 150 mm. of mercury. Immediately following the sectioning of the cord the pressure usually

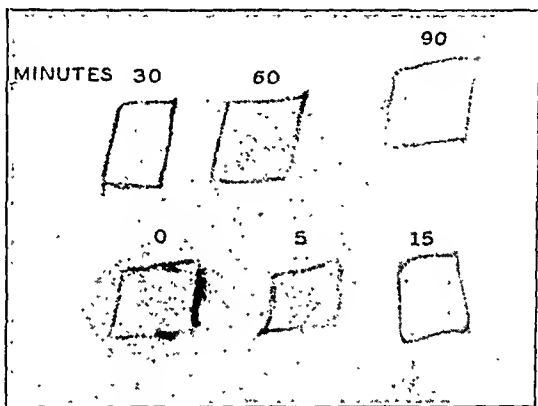


Fig. 1.—Xylene was carefully applied to areas of the skin of a normal rabbit at the time indicated before 10 cc. of trypan blue was injected intravenously. The largest amount of dye is present in the area where xylene was applied immediately before the dye was injected. There is no dye in the area where xylene was applied ninety minutes previously. The photograph was made ten minutes following the injection of the dye.

fell to approximately 50 mm. of mercury. During the following two or three hours, the pressure usually gradually increased, however, it again decreased, reaching a level of about 50 mm. of mercury or even lower within a period of five or six hours. There was essentially no variation in the level of the blood pressure over a period of six hours in 2 control rabbits.

Xylene was carefully applied to local areas of the skin of 10 rabbits in which the spinal cord was cut. The macroscopic reactions in the skin varied in the different rabbits. In some, the reaction developed the same as it did in the normal animals, while in others the reaction was either decreased or completely absent. This decrease in the inflammatory reaction occurred in the rabbits with a low

blood pressure. There appeared to be a definite correlation between the degree of reaction in the skin and the level of the blood pressure.

Trypan blue was injected intravenously into these rabbits. In the controls the dye localized and concentrated first in the area where xylene was applied for the shortest interval before the dye was injected (fig. 1). There was a gradual diminution in the quantity of dye that localized in the xylene-treated areas as the interval between the application of the irritant and the injection of the dye increased. Essentially the same amount of dye localized and concentrated in the areas of skin treated with xylene three hours before the dye was injected as localized in the untreated skin. The dye always localized in the xylene-treated areas of skin within a period of five minutes following the injection.

The following protocol of rabbit 693 shows the failure of trypan blue to localize and to concentrate in xylene-treated areas of skin in rabbits with the spinal cord cut and with an abnormally low blood pressure.

- 11:30 a. m. Cervical portion of cord cut.
- 11:31 a. m. Xylene applied to skin in area 1.
- 11:45 a. m. Area 1 was hyperemic.
- 1:45 p. m. The hyperemia in area 1 apparently was decreasing.
- 1:50 p. m. Blood pressure, 34 mm. of mercury.
- 3:00 p. m. Xylene applied to area 2.
- 3:15 p. m. Xylene applied to area 3; 10 cc. of trypan blue given intravenously; there was no hyperemia or edema in areas 2 and 3.
- 3:25 p. m. No trypan blue in any of the xylene-treated areas of skin.

In the rabbits with a slightly higher blood pressure than that shown, erythema and edema occurred; however, the condition was decreased from that in the normal rabbit. The pattern of the localization and concentration of trypan blue also was different in these rabbits from that of the normal as shown by the following protocol of rabbit 709:

- 10:30 a. m. Cervical portion of cord cut; xylene applied to area 1.
- 12:00 noon. Xylene applied to area 2.
- 1:00 p. m. Xylene applied to area 3.
- 1:30 p. m. Xylene applied to area 4.
- 1:45 p. m. Xylene applied to area 5.
- 2:00 p. m. Xylene applied to area 6; 10 cc. of trypan blue given intravenously.
- 2:05 p. m. Dye in areas 4 and 5 (fig. 2A).
- 2:20 p. m. Dye in areas 4 and 5; less dye in area 6 than in area 5; less dye in area 3 than in area 4.
- 2:30 p. m. Dye in areas 3, 4, 5 and 6 (fig. 2B).
- 4:00 p. m. Essentially the same amount of dye in areas 4, 5 and 6; there was less dye in area 3 than in area 4; no dye present in areas 1 and 2 (fig. 2C).
- 4:15 p. m. Killed; sections removed for histologic study.

These experiments indicated that the development of the macroscopic changes in inflammation and the localization and the concentration of trypan blue in areas of inflammation are affected by the level of the blood pressure.

Sections of skin treated with xylene and areas injected with both aleuronat and staphylococci from 15 rabbits in which the cervical portion of the spinal cord was cut were studied. The interval between the injection of these irritants varied from two to six hours. There was a decrease in the leukocytic reaction in the rabbits with a low blood pressure as compared with the rabbits with a normal pressure. The rabbits with a low pressure failed to have any leukocytes around the irritants (fig. 3).

These experimental observations suggest that the sectioning of the spinal cord in the cervical region did not directly affect either the localization of trypan blue

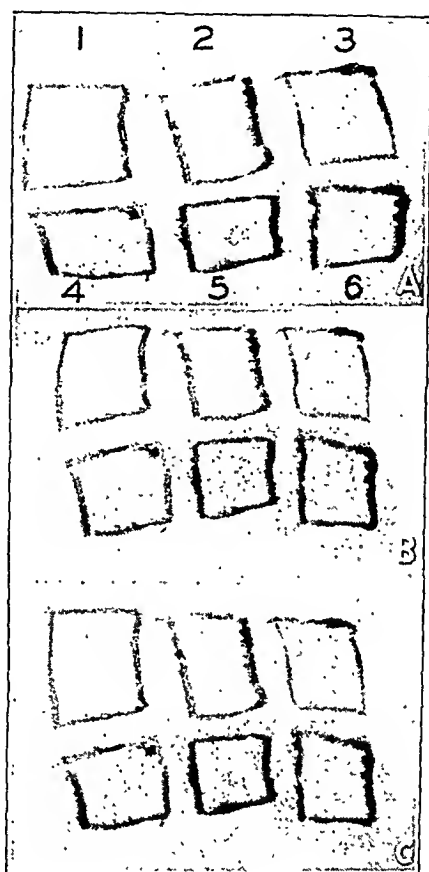


Fig. 2.—The cervical cord of this rabbit (709) was completely severed preceding the application of xylene to the areas of skin. Xylene was applied to area 1, three and a half hours before dye was injected; area 2, two hours; area 3, one hour; area 4, thirty minutes; area 5, fifteen minutes and area 6, immediately before. *A*, trypan blue is present only in areas 4 and 5 after five minutes. *B*, dye is present only in areas 3, 4, 5 and 6; photograph was made after thirty minutes. *C*, dye is present only in areas 3, 4, 5 and 6; areas 1 and 2 are hyperemic at this time. The photograph was taken two hours after the dye was injected.

or the localization of polymorphonuclears in areas of inflammation except secondarily as the result of the lowering of the blood pressure. The spinal cord was sectioned in the lumbar region of 7 rabbits in order to study the development of the

inflammatory reaction. Aleuronat and staphylococci were injected intradermally at intervals of six, four and two hours before the rabbits were killed. Clinically, the rabbits did not appear to be in shock. The blood pressure remained normal in those in which it was recorded. There was no difference in either the macroscopic or the microscopic reaction in these rabbits and that which occurred in the normal animals.

The leukocytes were counted in the blood from the ear of 3 rabbits both before and after the cervical portion of the spinal cord was cut. There occurred a diminution in the total white blood cell count immediately following the cutting of the cord; however, this variation was not outside the range of normal. It appears, therefore, that the failure of leukocytes to localize and to concentrate in

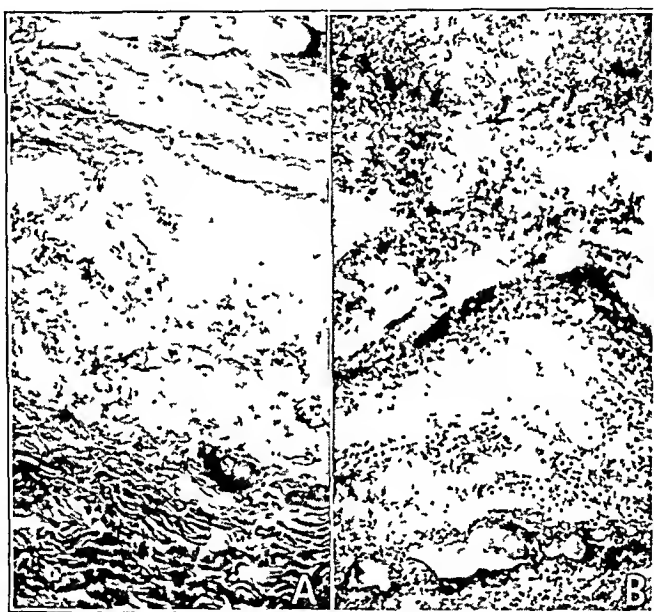


Fig. 3—*A*, photomicrograph of a section removed from rabbit 387 four hours after the intradermal injection of 0.2 cc. of staphylococci. This rabbit's spinal cord was cut; the blood pressure was 50 mg. of mercury. The rabbit appeared to be in shock. Note the clumps of bacteria and the absence of leukocytes. *B*, photomicrograph of a section from rabbit 309, which served as a control for 387. There is a diffuse infiltration of the area with leukocytes.

areas of inflammation in these rabbits cannot be explained by an absence of white cells among the circulating cells.

#### COMMENT

Trypan blue localized and concentrated in the xylene-treated area of skin in the rabbits with the spinal cord severed at the level of the seventh cervical vertebra, if the blood pressure was normal, in a manner similar to that in normal rabbits. In contrast to this observation, the



dye failed to localize and to concentrate in the xylene-treated areas of skin in rabbits in which the cord was cut at the same level, and the blood pressure was markedly decreased. These observations suggest, therefore, that the variation in the localization and the concentration of trypan blue in the skin of rabbits following the cutting of the spinal cord is determined by the level of the blood pressure and is not influenced by the nerves.

Polymorphonuclear leukocytes failed to concentrate in the areas of skin injected with both aleuronat and staphylococci when the blood pressure was markedly decreased. The failure of leukocytes to concentrate in the areas of inflammation in the rabbit with the spinal cord cut in the cervical region and with an accompanying low blood pressure suggests that this same phenomenon may explain the failure of the leukocytes to concentrate in the skin of the rabbits given large amounts of epinephrine, sick following the intravenous injection of staphylococci and also with a low blood pressure following hemorrhage. It has been suggested that edema fails to develop and leukocytes fail to concentrate in the skin of rabbits in shock due to the constriction of the cutaneous vessels.<sup>6</sup> Unless clinical evidence of shock develops and the blood pressure is markedly decreased, the inflammatory reaction develops the same in animals with the spinal cord cut as in the controls.

Section of the lumbar cord may lower the blood pressure some; however, it rarely produces the profound picture of shock that frequently results from the cutting of the cord at the level of the seventh cervical vertebra. The degree of fall in the blood pressure following the cutting of the cervical cord is variable, as shown by the studies of Wilson, Roome and Grimson<sup>7</sup> on dogs. The present experiments show that similar variations occur in the rabbit.

The vasodilation in the skin that usually occurs either following the cutting of the spinal cord or the removal of the sympathetic ganglions in specific areas of the body apparently has little if any effect on either the localization of trypan blue or the concentration of polymorphonuclear leukocytes as demonstrated by this technic. It is suggested that the diminution in the inflammatory reaction as observed by Lauer<sup>1</sup> may be explained by a decrease in the blood pressure. This assumption is supported by his observation that the inflammatory reactions were similar above and below the severed segment. Furthermore, Lauer did not think that this diminished reaction could be ascribed to either the separation of the organ from its nervous centers or loss of pain sensations.

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7. Wilson, H.; Roome, N. W., and Grimson, K.: Complete Sympathectomy: Observations of Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs, *Ann. Surg.* **103**:498 (April) 1936.

## SUMMARY

The skin of the rabbit fails to show hyperemia and edema following the local application of xylene when the cervical portion of the spinal cord is cut, if the animal is also in shock.

Trypan blue fails to localize and to concentrate in the xylene-treated areas of skin of rabbits when they are in shock.

Polymorphonuclear leukocytes also do not concentrate in areas of skin injected with either staphylococci or aleuronat when the spinal cord is cut and the animals are in shock.

The sectioning of the spinal cord in the rabbit apparently has no direct effect on the development of the local inflammatory reaction provided the animals are not in shock as the result of the sectioning of the cord.

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# PERINEPHRIC ABSCESS

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Suppuration in the perinephrium is of special importance because of the morbidity and mortality rates associated with the lesion. The disease is not uncommon. In the twenty-eight years since the first patient was admitted to the Peter Bent Brigham Hospital, 66 patients have been treated who were found to have perinephric abscess either alone or complicating other diseases. In addition, there were 6 other patients in whom the signs and the symptoms were most suggestive of perinephric abscess. They recovered without operation, however, and the diagnosis was consequently never proved.

The difficulties of diagnosis and the problems of treatment in patients ill because of perinephric abscess have been emphasized repeatedly in the literature.<sup>1</sup>

It was thought, therefore, that analysis of the cases to be described would yield data to help solve the many problems presented by infection in the perinephrium.

## DEFINITION AND TERMINOLOGY

Perinephric abscess is a suppurative inflammatory lesion of the perinephrium, the fibrofatty bed surrounding the kidney in the lumbar gutter. The anatomy of this region was admirably described and illustrated by Gerota in 1895.<sup>2</sup> Confusion has existed in the past because of variation in the terminology used by writers. The term "paranephric abscess" should properly be reserved for lesions in the paranephric fat outside the fascia of Gerota. Such an isolated lesion is unusual, and recognition of it before operation is difficult. For clinical purposes, it is best to consider the surgical perinephrium as including anatomically both perinephrium and paranephrium. In thus simplifying the nomen-

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1. (a) Miller, M. B.: Perinephric Abscess, *Ann. Surg.* **51**:382-415, 1910. (b) Mathé, C. P.: Diagnosis and Treatment of Perinephric Abscess: Renal Fixation, a New Roentgenographic Diagnostic Sign, *Am. J. Surg.* **38**:35-49, 1937. (c) Foulds, G. S.: Diagnosis of Perinephric Abscess, *J. Urol.* **42**:1-4, 1939. (d) Atcheson, D. W.: Perinephric Abscess with a Review of One Hundred and Seventeen Cases, *ibid.* **46**:201-208, 1941.

2. Gerota, D.: Beiträge zur Kenntnis des Befestigungsapparates der Niere, *Arch. f. anat. u. Entwicklungsgesch.*, 1895, pp. 265-285.

clature, the surgical significance of Gerota's fascia in the spread of infection about the kidney and in the symptoms resulting therefrom need not be minimized. "Perinephritic abscess" has been suggested as applicable to those conditions secondary to primary disease in the kidney.<sup>3</sup> The long accepted use of the term "nephritis," however, for an entity not related to active suppuration in the kidney makes the use of the term "perinephritic" unfortunate because of the connotation. "Perirenal abscess" has often been employed in the past. The term should be abandoned because of its impure composition, since it is derived from both Greek ("peri-") and Latin ("renal"). "Perinephric abscess" is an adequate term if one qualifies it as either "simple" (due to metastatic infection involving the perinephrium directly or secondarily

TABLE 1.—*Classification of the Cases of Perinephric Abscess*

Group	Cases
I. Simple perinephric abscess.....	34
A. Without gross evidence of infection of the kidney *.....	25
B. With evidence of abscess or carbuncle of the kidney.....	9
II. Complicated perinephric abscess.....	32
A. Secondary to renal calculus and pyelonephritis.....	12
B. Secondary to severe pyelonephritis.....	8
C. Secondary to pyonephrosis.....	5
1. Due to ureteral calculus.....	2
2. Due to carcinoma of the prostate.....	2
3. Due to carcinoma of the bladder.....	1
D. Secondary to disease in the juxtarenal tissues.....	7
1. Tuberculosis of the spine.....	3
2. Actinomycosis of the lung and the spine.....	1
3. Amebic abscess of the liver.....	1
4. Appendical abscess.....	1
5. Ruptured diverticulum of the descending colon.....	1

\* In this group was included a case secondary to rupture of the kidney.

from abscesses in the kidney) or "complicated" (due to acute or chronic infection in the kidney itself or in the juxtarenal tissues).

#### CLASSIFICATION OF PERINEPHRIC ABSCESS

A classification of perinephric abscess on an etiologic basis is the most convenient. The lesion is always secondary to infection elsewhere in the body. In this report, the lesions which have reached the perinephrium from distant foci by way of the blood stream or the lymphatics will be designated simple perinephric abscess. Included in this group will be those lesions in which infection has reached the perinephrium by extension from metastatic carbuncle or abscess of the kidney. Those reaching the perinephrium by direct extension from diffuse pyelonephritis or pyonephrosis or by direct or lymphatic extension from adjacent or nearby foci will be called complicated perinephric abscess. Table 1 is a classification of the cases to be described in this paper.

3. Vermooten, V.: The Mechanism of Perinephric and Perinephritic Abscess: A Clinical and Pathological Study, *J. Urol.* 30:181-193, 1933.

## INCIDENCE

Perinephric abscess is not a rare disease. On an active surgical service of some 100 beds at the Peter Bent Brigham Hospital, about 4 patients with perinephric abscess are treated each year.

TABLE 2.—*Symptoms of Sixty-Six Patients with Perinephric Abscess*

Symptoms	Cases
Pain .....	64 (out of 66)
Nausea and vomiting.....	35
Simple perinephric abscess.....	9 (out of 34)
Complicated perinephric abscess.....	18 (out of 24)
Urinary complaints .....	33 (out of 66)
Simple perinephric abscess.....	11 (out of 34)
Frequency and nocturia.....	6
Dysuria .....	5
Complicated perinephric abscess (due to acute and chronic sepsis in the kidney).....	21 (out of 25)
Frequency and nocturia.....	18
Pyuria .....	9
Dysuria .....	5
Hematuria (due to juxtarenal disease).....	1
Nocturia .....	1 (out of 7)

TABLE 3.—*Incidence of Antecedent Infection in Thirty-Four Cases of Simple Perinephric Abscess*

	Cases
Infections of the skin and the subcutaneous tissues.....	9
Acute infections of the upper part of the respiratory tract*.....	6
Pulmonary suppuration (bronchiectasis).....	2
Thrombophlebitis with abscess formation.....	1
Postpartum infection .....	1

\* In 1 of these cases there was severe tonsillitis.

TABLE 4.—*Age Incidence of Perinephric Abscess*

Type of Abscess	Mode	Youngest *	Oldest	Average
Simple.....	25 to 35 yr.	15 yr.	60 yr.	34 yr.
Complicated.....	40 to 50 yr.	22 yr.	77 yr.	47 yr.

\* Patients under 12 were not admitted to the hospital.

TABLE 5.—*Laterality and Sex Incidence of Perinephric Abscess*

Type	Right	Left	Male	Female
Simple.....	21	13	24	10
Complicated.....	16	17	17	15
Due to calculi.....	6	6	4	8
Due to pyelonephritis*.....	4	5	2	6
Due to pyonephrosis.....	2	3	5	0
Due to juxtarenal disease.....	4	3	6	1

\* One patient had bilateral perinephric abscesses.

*Age.*—The disease is uncommon in infants and children, presumably because these have as yet poorly developed perinephric tissues. In

adults, the age incidence differs with the type of perinephric abscess (table 4). The majority of cases of simple perinephric abscess occur between the ages of 25 and 35. Only 2 of the 34 patients were under 20. Complicated perinephric abscess, however, occurs most commonly in the late fourth and fifth decades. The patients in whom the abscess was secondary to pyonephrosis were all over 50 years of age (average age, 63).

*Sex.*—The statement is sometimes made that perinephric abscess is rare among female patients. The data from this study indicate the importance of segregating the cases into the two main groups, simple and complicated. In the former group, the ratio of male to female patients was  $2\frac{1}{2}$  to 1. In the group in which the abscess was secondary to renal calculi and to pyelonephritis, however, the ratio was reversed (table 5). Those secondary to pyonephrosis happen to have been all in male patients.

*Laterality.*—Simple perinephric abscess was nearly twice more common on the right side than on the left. In the complicated variety, however, the lesion was encountered on one side as frequently as on the other.

#### DIAGNOSIS

The diagnosis of perinephric abscess is made by integration of the data obtained from the history, the physical examination, the laboratory studies and the roentgen examinations.

*History.*—Early in the development of perinephric infection, the patient may have no specific complaints. He may recall that he had a skin infection or a severe infection of the upper part of the respiratory tract several days or even weeks before the visit and that he had felt "below par" ever since then. Anorexia, easy fatigability and night sweats are common early complaints.

A history of chills and fever was common. All the 34 patients with simple perinephric abscesses had objective fever, and 31 had complained of subjective fever. Seventeen of the 34 had had shaking chills one to several times. Among the 12 patients with perinephric abscess secondary to renal calculus, only 3 had had shaking chills. All complained of having been feverish, and all but 1 had objective fever. Of the 7 patients with abscess due to juxtarenal infection, 3 had had shaking chills. Five complained of subjective feverishness. Two had neither subjective nor objective fever.

Antecedent infection was recorded in 19 of the 34 cases of simple perinephric abscess (table 3). Twelve others of the 34 patients were found to have teeth "in wretched condition," but they had not complained of them. Perinephric abscess developed in 1 patient after

traumatic laceration of the kidney with extravasation of blood and urine but without a history of previous infection. The source of infection in the group of cases of complicated perinephric abscess is obvious. Whether the abscess formation in these cases was due merely to slow progression and extension of the renal infection or to flare-up of sepsis due to intercurrent infection could not be determined from this series. In 1 case, however, symptoms of perinephric abscess began one day after the onset of infection in the upper part of the respiratory tract.

Pain is the most common and sometimes the earliest specific symptom (table 2). It was absent in only 3 cases from the entire series of 66. These were complicated abscesses secondary to diabetic gangrenous pyelonephritis (1 case) and to obstructed pyonephrosis (2 cases). The pain was never colicky, but it did vary in intensity. In fact, it sometimes disappeared for periods of two or more days only to return with increased severity. Sometimes the pain was brought out only with motions of the trunk, with deep breathing or on coughing. Three patients in this series volunteered the information that the pain was relieved by flexing the thigh. Two of these kept the thigh flexed constantly.

The location of pain varied. Most commonly it was situated in the loin. The radiation of pain was of special interest because of its relation to the site of the lesion. Radiation of pain into the upper quadrant of the abdomen was especially common in those cases in which abscess was secondary to renal calculus. Six of 12 such patients complained of pain in the upper quadrant of the abdomen as well as in the loin and the costovertebral angle region. This may have been due to the almost uniform inflammatory involvement of the tissue about the renal pelvis both anteriorly and posteriorly in the presence of renal calculi. Two patients with simple perinephric abscess complained of pain in the ipsilateral shoulder. In these, the abscess overlay the upper pole of the kidney. Three patients complained of radiating pain down the anterolateral aspect of the thigh to the level of the knee due to irritation of the lumbar plexus by the perinephric abscess located posteromedially. In 2 other cases there was radiation of the pain into the ipsilateral testis.

In several cases, the pain radiated into the lower quadrant of the abdomen. Two patients with simple perinephric abscess complained of pain only in the right lower quadrant of the abdomen. One of these exhibited a palpable mass suggesting an appendical abscess. In each, the lesion involved the perinephrium anteriorly only.<sup>4</sup> These lesions are of special importance because of their not infrequent confusion with appendicitis.

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4. Vergoz and Lenck: Du phlegmon périnéphrétique antérieur, *J. d'uro.* 47:369-394, 1939.

Nausea and vomiting were common only in the cases of abscess secondary to chronic disease of the kidney. Of 26 patients with this condition, 20 complained of moderate to severe nausea and vomiting. On the other hand, among the 35 patients with simple perinephric abscess, only 9 had gastrointestinal complaints.

Urinary symptoms were uncommon in the cases of simple perinephric abscess. Of the 34 patients with this condition, only 6 complained of frequency and nocturia, and 5, of dysuria. These symptoms were never prominent. Likewise, among the patients with perinephric abscess secondary to juxtarenal disease, only 1 complained of occasional nocturia. Of 25 patients with complicated perinephric abscess with primary disease in the kidney, however, 21 had prominent urinary symptoms (table 2). It appears, then, that perinephric abscess does not cause urinary symptoms but that when these are present, they are secondary to infection within the urinary tract itself.

Loss of weight is often a prominent observation in patients ill with perinephric abscess. This is true not only of those in whom chronic renal infection has existed for a long time but also among those with simple perinephric abscess of relatively short duration. One patient with perinephric abscess secondary to renal calculus had lost 60 pounds (27.2 Kg.) during the preceding year and 33 pounds (15 Kg.) during the preceding month. A 32 year old previously robust woman lost 32 pounds (14.5 Kg.) during the six weeks before admission to the hospital, and a 26 year old physician lost 25 pounds (11.3 Kg.) during an illness of only four weeks.

*Physical Findings.*—The patient with perinephric abscess looks acutely ill. This is particularly true of those with simple perinephric abscess. In the group with complicated abscess, the picture is more one of chronicity and debilitation, owing to the combined effects of prolonged sepsis and renal insufficiency. Night sweats are the rule; the skin presents a pasty pallor. In the acute condition the patient is apprehensive; those with complicated perinephric abscess are often apathetic. Toxicity and prostration characterize the former group; wasting, apathy and even coma characterize the latter. Patients with complicated abscess who present themselves during an acute exacerbation of nephric and perinephric infection, however, may show a degree of toxicity equal to that of patients with acute simple perinephric abscess.

*Temperature:* The degree of fever in patients with perinephric abscess is variable. The morning temperature is sometimes normal, but it rises in the afternoon and the evening to a level varying between 102 and 106 F. orally. It is generally not spiking, however, except during the early phase of the disease—probably before inflammatory fixation has taken place.



**Pulse Rate:** Occasionally, the pulse rate of patients with perinephric abscess was recorded as within normal limits. Usually, however, depending largely on the severity of the infection and the debility of the patient, the pulse rate was elevated to as high as 140. It was seldom below 90.

**Tenderness:** Tenderness was the most common finding on physical examination. Among the 34 patients with simple perinephric abscess, 24 had tenderness on pressure in the costovertebral angle; on pressure on the twelfth rib and sometimes on pressure over the eleventh rib. Nine of the 10 remaining patients in this group exhibited tenderness in the loin. The other had tenderness only in the right lower quadrant of the abdomen extending outward toward the flank. This was a patient with an anterior perinephric abscess due to beta hemolytic streptococci following an acute infection of the upper part of the respiratory tract.

In 13 of the 34 cases of simple perinephric abscess, tenderness extended into the upper part of the abdomen. In 7, it was found in the lower part. These are the cases in which the possibility of cholecystitis and appendicitis must be ruled out.

Tenderness was an equally prominent finding in patients with complicated perinephric abscess. It was most commonly located in the flank and the costovertebral angle. Tenderness in the lower part of the abdomen was found in only 2 cases.

**Spasm:** Twenty-two of the 34 patients with simple perinephric abscess showed spasm in the flank. Nine of these had spasm in the region of the costovertebral angle as well. Most of the patients with tenderness extending into the upper and lower parts of the abdomen also had spasm in these areas, but the degree of this was variable.

Except in the cases secondary to juxtarenal disease, spasm was not as prominent in patients ill from complicated perinephric abscess. This may have been due to chronicity of the disease and relatively greater debility of the patients. Of the 7 patients with perinephric abscess complicating adjacent infection, however, 6 showed both tenderness and spasm in the flank.

**Palpable Mass:** Visible swelling in the loin was observed in 21 of the 34 cases of simple perinephric abscess, in 6 of the 12 cases secondary to renal calculus, in 3 of the 8 cases due to pyelonephritis without calculus and in 3 of the 7 cases complicating juxtarenal disease. A distinct mass, however, was palpable in only some of these, i. e., in about one third of the cases of simple abscess and half the cases due to renal calculus (table 6). Each 1 of 8 patients with abscess due to pyelonephritis showed a palpable mass on physical examination even though there was no visible swelling in the flank. Occasionally, edema and tenderness were observed in the skin, and subcutaneous tissue overlying

the mass was noted. Of special interest is the fact that a large proportion of the palpable masses moved with respiration (table 6). Abscesses in other locations, such as appendical abscess, are usually fixed. In cases of perinephric abscess, mobility of the mass probably indicates the presence of relatively free layers of paranephric fat.

**Changes in the Diaphragm:** Physical examination of the chest revealed elevation of the ipsilateral diaphragm in 7 cases. Three of these cases were among the 12 patients in whom the disease was secondary to renal calculus. The others were among the patients with simple perinephric abscess. In all but 1 the abscess involved the perinephrium overlying the upper pole of the kidney.

**Scoliosis:** Curvature of the spine with concavity toward the side of the lesion due to spasm of the paravertebral muscles has been emphasized as a prominent sign of perinephric abscess. Scoliosis was detected clinically in only 4 of the 66 cases of perinephric abscess. They were all in patients with simple abscesses. One of them walked with an obvious list toward the affected side. By roentgen examination,

TABLE 6.—*Palpable Mass in Perinephric Abscess*

Group	Cases	Visible Swelling	Palpable Mass	Movable Mass
Simple.....	34	21	10	1
Complicated.....	32	14	18	7
Due to renal calculus.....	12	6	6	4
Due to juxtarenal infection.....	7	3	3	1
Due to pyelonephritis.....	8	5	8	2
Due to pyonephrosis.....	5	0	1	0

definite mention of scoliosis was made in only 2 cases. It seems, then, that though of significance when found, scoliosis is one of the less common signs of perinephric abscess.

**Spasm of the Psoas Muscle:** The proximity of the psoas muscle to the perinephrium renders it especially subject to involvement by inflammatory reactions about the kidney. The frequency with which patients volunteered the information that they were more comfortable with the thigh flexed has already been mentioned. Yet gross evidence of spasm in the psoas muscle was encountered only seldom. In this series it was recorded in only 2 of the 66 cases. In 1 patient, the perinephric abscess was secondary to inflammation and perforation of a diverticulum of the descending colon; in the other, it was secondary to acute and chronic pyelonephritis. The latter patient had to keep her thigh constantly flexed for relief of pain.

**Roentgen Examination.**—The information secured by roentgen examination of the patient suspected of having perinephric abscess is an important adjunct, when properly interpreted, to the data obtained

by other methods of investigation. However, none of the accepted roentgen signs of perinephric abscess is sufficiently pathognomonic to rule the lesion in or out. Perinephric abscess may exist in the absence of any abnormality in the roentgen film or may be absent in the presence of one or more signs known to accompany the lesion.

The incidence of positive roentgen findings is recorded in table 7. It will be noted that among the cases studied, in about one third there was no definite abnormality in the roentgenogram of the abdomen. Indistinctness of the ipsilateral psoas margin with a normal shadow on the opposite side was the most common finding in both the simple and the complicated types of abscess. Elevation of the diaphragm was found in 5 of the 28 cases of simple perinephric abscess and in 6 of the 12

TABLE 7.—Roentgen Findings in Sixty-One Cases of Perinephric Abscess

Type	Total	Patients Studied Roentgenologically	Negative Kidney, Ureter and Bladder Film	Obliteration of Psoas Shadow with Opposite Side Normal	Elevation of Diaphragm with Limitation of Respiratory Excursions	Pyelographic Changes	Scoliosis	Soft Tissue Mass in the Flank
Simple.....	34	28	10	8	5	6	2	0
Without abscess of the kidney.....	25	21	8	6	4	4	1	0
With abscess of the kidney.....	9	7	2	2	1	2	1	0
Complicated.....	27	23	5	5	4	..	1	4
Secondary to renal calculi.....	12	11	0	2	4	Associated with calculus	0	2
Secondary to pyelonephritis.....	8	5	2	0	0	..	0	1
Secondary to juxta-renal infection.....	7	7	3	3	0	..	1	1

cases of complicated abscess secondary to renal calculi. In all of them, the lesion was either localized to the region overlying the upper pole of the kidney, or it involved the perinephrium diffusely about the kidney in addition to the region adjacent to the upper pole. Two of the patients with an elevated diaphragm showed a small pleural effusion on the same side.

**Pyelographic Examination:** Excretory pyelograms demonstrated changes in 6 of the 10 cases of simple perinephric abscess in which the test was made. The abnormalities recorded were distortion of the calices to resemble polycystic disease of the kidney, rotation of the kidney in either its horizontal or vertical axis, lateral or medial displacement of the kidney and the upper end of the ureter and compression of the calix and the renal pelvis (due to carbuncle of the kidney).

Similar changes were seen in roentgenograms of patients with perinephric abscesses secondary to renal calculi. Of special interest is the fact that in 2 of the 11 cases studied, the renal shadow on the affected side was described as abnormally small. In 7 of the 28 cases of simple perinephric abscess studied, however, the renal shadow was abnormally large. Soft tissue masses were visualized in 4 of the patients with complicated perinephric abscess but in none of those with simple perinephric abscess. Positive findings were obtained in 4 of the 7 cases secondary to juxtarenal disease (table 7).

*Laboratory Data.*—Urinalysis: In table 8 are recorded the findings on examination of the urine of 66 patients with perinephric abscess. Here again it is important to note the differences among the various types of perinephric abscess. Abnormalities are least frequent in patients with simple perinephric abscess who at operation had no gross evidence

TABLE 8.—*Urinalysis in Cases of Perinephric Abscess.\**

Type of Abscess	Albumin					White Blood Cells †					Red Blood Cells †				
	0	+	2+	3+	4+	0	+	2+	3+	4+	0	+	2+	3+	4+
Simple (24 cases)															
Without evidence of abscess in the kidney.....	24	0	0	0	0	9	5	8	2	..	17	7	..	..	..
With abscess in the kidney	6	1	2	..	..	1	8	..	..	..	2	6	..	..	..
Complicated															
Due to renal calculus (12 cases).....	1	1	1	9	..	0	2	10	..	..	1	6	3	2	..
Due to pyelonephritis (8 cases).....	2	6	..	..	..	..	..	..	8	..	..	..	..	4	..
Due to juxtarenal disease (7 cases).....	4	1	1	1	..	3	3	..	1	..	5	1	1	..	..

\* Cases secondary to pyonephrosis not included.

† 0 = none; + = scarce; 2+ = few; 3+ = many; 4+ = very many.

of abscess in the kidney itself. None of these patients, for instance, showed albuminuria; only 7 of them showed a rare red blood cell in the urinary sediment, and 15 showed rare to many white blood cells.

The urine of patients who at operation showed evidence of renal involvement, however, showed relatively more abnormal elements in the urine. Two thirds of them had albuminuria, and all but 1 showed at least some white blood cells in the urine. The greatest abnormality was found in the urine of patients with complicated perinephric abscess (table 7).

*Cytologic Character of the Blood:* Hypochromic anemia was found frequently, particularly in the patients with complicated perinephric abscess. These had been ill for longer periods, and the anemia was correspondingly more prominent.

The white blood cell count was almost invariably elevated. A normal count was obtained in only 1 patient. She was extremely ill with

perinephric abscess secondary to pyelonephritis, and examination of the blood smear showed 92 per cent polymorphonuclear cells with a marked shift to the left. In cases of simple perinephric abscess without evidence of abscess in the kidney, the average white blood cell count was 19,500; in the cases in which there was abscess in the kidney itself, the average white blood cell count was 14,200. The highest count in the group with simple perinephric abscess was 40,000. Higher white blood cell counts were obtained in patients with complicated perinephric abscess. The highest was 84,000 cells per cubic millimeter (obtained repeatedly and in the absence of leukemia); it was that of a patient with perinephric abscess and renal calculi. The next highest count (56,900) was that of a patient with perinephric abscess secondary to pyelonephritis without calculi.

TABLE 9.—*Bacteriologic Findings in Sixty-Six Cases of Perinephric Abscess*

Group	Cases	Staph. Aureus	Staph. Albus	B. Coli	Mixed	Str. Haemolyticus	Nonhemolytic Streptococcus	Tuberculosis	Actinomycosis	Cases in Which Blood Cultures Were Made	Cases in Which Blood Cultures Were Positive
Simple perinephric abscess.....	34	23	4	0	0	2	1	..	..	2	1
Without abscess of the kidney.....	25	17	2	0	0	..	..	..	..	5	0
With abscess of the kidney.....	9	6	2	0	0	..	..	..	..	2	1
Complicated perinephric abscess.....	32	1(?)	1	14	6	..	..	..	..	5	0
Due to renal calculus.....	12	1(?)	..	6	2	..	..	..	..	2	0
Due to pyelonephritis.....	8	..	1	5	..	..	1	..	..	1	0
Due to pyonephrosis.....	5	..	..	2	1	..	..	..	..	1	0
Due to juxtarenal disease.....	7	..	..	1	2*	1	..	3	1	1	0

\*See text.

All the patients showed an increase in the proportion of polymorphonuclear cells in the blood. The majority showed a differential count of 85 to 90 per cent polymorphonuclear white blood cells. The highest was 97 per cent. The erythrocyte sedimentation rate was determined in 2 patients and was markedly elevated in both.

*Bacteriologic Findings.*—Culture of the perinephric pus from patients with simple perinephric abscess showed bacteria almost always in pure culture. The most common organism recovered was Staphylococcus aureus (in 23 of the 34 cases of simple perinephric abscess). Staphylococcus albus was recorded in 4 of the other 11 cases. In 2 cases a growth of beta hemolytic streptococcus was obtained, and in 1 case, nonhemolytic streptococci were cultured. No bacteriologic data were available for 3 patients, and in 1 instance there was no growth in cultures of the exudate in routine mediums.

Cultures were made of the venous blood of 8 patients with perinephric abscess, without renal involvement in 5 and with abscess of the kidney in 3. None of the former were positive; among the latter, 1 showed a growth of *Staph. aureus* and *Bacillus coli*, and 2 were sterile.

Cultures of the pus from perinephric abscesses secondary to calculus disease of the kidney showed *B. coli* in pure cultures in 6 of the 12 cases. In 2 other cases, this organism was found together with staphylococcus (*Staph. aureus* in 1 and *Staph. albus* in the other). No growth was obtained in the culture from 1 case. The colon bacillus was likewise the predominating organism in the case secondary to noncalculous pyelonephritis and to pyonephrosis (table 10).

In the cases secondary to juxtarenal disease, the organisms cultured were the same as those in the primary lesions. Two of the 7 patients showed *B. coli* (1 in conjunction with an unidentified coccus). Three

TABLE 10.—*Morbidity in Sixty-Six Cases of Perinephric Abscess*

Type of Abscess	Simple Perinephric Abscess		Complicated Perinephric Abscess			
	Without Abscess of the Kidney	With Abscess of the Kidney	Due to Renal Calculi	Due to Pyelonephritis	Due to Pyonephrosis	Due to Juxtarenal Disease
Operations.....	1 to 2	1 to 3	1 to 3	1 to 2	1 to 2	1
Average number of days in the hospital postoperatively.....	24	69	53	25.5	73 to 99 †	40
Mortality (percentage of subgroup)*.....	0	0	33	50	50†	14

\* Deaths due to uremia because of progressive irreparable damage to the kidneys have not been included in this group. The perinephric abscess in these cases was only a minor incident. A patient with perinephric abscess and carbuncle of the kidney accompanying brain abscess and purulent (*Staph. aureus*) meningitis also has been excluded.

† Includes only the 2 patients who were operated on.

‡ Only 2 of the 5 patients in this group could be considered suitable for this analysis. One died after drainage first of the abscess and then of the kidney. The other was cured after incision and drainage of the abscess followed by nephrectomy.

cases were due to tuberculosis, and 1 patient showed a mixed growth of *Streptococcus haemolyticus* and *Staph. aureus*. *Endamoeba histolytica* was the causative agent in 1 case secondary to amebic abscess of the liver, and actinomyces was recovered from another patient.

#### TREATMENT OF PERINEPHRIC ABSCESS AND RESULTS

Six patients suspected of having had perinephric abscess were not included in the analysis just given because they recovered without operation and the diagnosis consequently was never proved. None returned to the hospital for recurrence of symptoms. These and similar cases reported in the literature indicate that spontaneous healing of perinephric abscess may occur, but it is the exception rather than the rule.

In 22 of the 24 cases of simple perinephric abscess without carbuncle of the kidney, the disease was cured by mere incision and drainage of the abscess. In 1 case, however, revision of the wound was required

to improve drainage, and in the other (secondary to traumatic injury of the kidney) nephrectomy was required twenty-six days after incision and drainage of the abscess.

Seven of the 9 patients who had perinephric abscess accompanied by abscess in the kidney were cured by simple incision and drainage. One of the 9 required nephrectomy five months after the initial incision and drainage because of persistent sepsis in the kidney. One of the patients in this group died without operation. He was a patient in whom a small (2.5 cm.) perinephric abscess and a cortical abscess of the kidney complicated *Staph. aureus* and *B. coli* bacteremia following sepsis in a laparotomy wound and thrombophlebitis with abscess formation in the leg. In addition, he had chronic glomerulitis and died in uremia.

Nephrectomy was done more frequently in the patients ill with complicated perinephric abscess. Four of the 12 patients with abscess secondary to renal calculus were treated by primary nephrectomy. Of these, 2 died—1 because of laceration of the diaphragm; the other because of persistent sepsis which eventually led to thrombophlebitis of the splenic vein and multiple liver abscesses. Four of the 12 patients were treated by incision and drainage followed by nephrectomy three weeks to three months later. All were cured of their disease.

Four patients with perinephric abscess secondary to renal calculi died after only incision and drainage of the abscess had been done. One was a 29 year old man who died of overwhelming infection twenty-five days after operation. His condition had apparently never been sufficiently good to warrant nephrectomy. One patient was 52 years old and died of a coronary attack during operation. Another was a 72 year old woman who recovered from incision and drainage of the abscess and was discharged home to continue her convalescence preparatory to secondary nephrectomy. She died at home a month later of coronary thrombosis. The fourth patient died in uremia shortly after revision of a draining sinus which had persisted after an operation for perinephric abscess three years previously. A similar patient with a draining nephrectomy sinus died in uremia without operation. She was 44 years old and had had renal calculi removed seven years previously.

All of the patients with perinephric abscess secondary to acute and chronic pyelonephritis were operated on. Four of the 8 were cured of the disease after nephrectomy. On 1, nephrectomy was done as a primary procedure; on the other 3 as a secondary operation eleven days, three and a half months and nine months after simple incision and drainage of the abscess. In the 4 that died, simple incision and drainage of the perinephric abscess was the only operative procedure except on the 2 patients with fulminating diabetic pyelonephritis (or gangrene of the kidneys), on whom in addition nephrostomy was done. The deaths are described in table 11.

TABLE 11.—*Hospital Deaths from All Causes Among Sixty-Six Patients with Perinephric Abscess*

Simple Perinephric Abscesses with Abscess in the Kidney						
Age	Sex	Operation	Interval Between Operation and Death		Autopsy	Comments
1*	50	M	None	.. . .	Yes	Cortical and perinephric abscesses were found only at postmortem examination; they were merely incidental to bacteremia and overwhelming sepsis from which the patient died (see text)
2*	40	M	Incision and drainage of perinephric abscess	5 days	Yes	In this patient the renal and perinephric abscess accompanied brain abscess and purulent meningitis from which he died; all the lesions were secondary to chronic bronchiectasis
Complicated Perinephric Abscesses						
A Due to Renal Calculi						
1	47	M	Nephrectomy on the right	.	Yes	Laceration of the diaphragm with perforation into the pleural cavity was the contributing cause of death
2	29	F	Incision and drainage of abscess	25 days	No	Died of persistent severe sepsis
3	57	F	Incision and drainage of abscess	Operative death	Yes	Patient died at close of operation, spinal anesthesia was used, cause of death not determined
4*	61	F	Revision of chronic draining sinus leading to abscess about the lower pole of the kidney	6 hours	Yes	Stones had been removed from the kidney 3 years previously, persistent sinus ever since; uremia from progressive renal failure; operation was done only as a last resort
5*	44	F	None	.	Yes	Perinephric abscess drained elsewhere, 7 years previously, persistent sinus ever since, progressively downhill uremic course during 6 weeks in the hospital
6	32	F	Nephrectomy	3 months	Yes	Died of persistent sepsis with thrombophlebitis of the splenic vein and multiple abscesses of the liver
B Due to Pyelonephritis						
1	21	M	Incision and drainage	3 days	No	Patient was ill with an unclassified hemorrhagic diathesis; kidney described as necrotic when abscess was incised and drained
2	61	F	Incision and drainage	Died during operation	No	Patient died, apparently of coronary thrombosis
3	46	F	Incision and drainage with nephrostomy	6½ hours	Yes	Patient had severe diabetes; kidneys actually gangrenous; progressive uremia, moribund before operation
4	46	F	Incision and drainage with nephrostomy	24 hours	Yes	Severe diabetes; acute and chronic pyelonephritis with bilateral multiple abscess formation; progressive uremia; operation done as last resort
C Due to Pyonephrosis						
1	62	M	1 Incision and drainage 2 Revision of wound and drainage of kidney	74 days after first and 24 days after second operation	Yes	Fecal fistula complicated incision and drainage of the abscess
2*	54	M	None	.	Yes	Died of perforation of carcinoma of the bladder into the general peritoneal cavity
3*	70	M	None	.	Yes	Died of renal failure with pyonephrosis and bilateral pyelonephritis; right perinephric abscess was incidental
4*	77	M	None	.	Yes	Carcinoma of the prostate; bilateral pyonephrosis; cortical abscess of both kidneys with perforation into the perinephrium on the left; progressive uremia was the cause of death
D Due to Juxtarenal Disease						
1	60	M	1 Incision and drainage of perinephric abscess 2 Drainage of iliopsoas abscess	43 days	Yes	Abscess was secondary to perforation of the diverticulum of the descending colon; fecal fistula developed 3 days before death; died of persistent sepsis and progressive debility

\* Not included in mortality statistics



The patients with perinephric abscess secondary to juxtarenal disease were all treated by incision and drainage alone. In 1 patient, sepsis extended along the iliopsoas bursa and required drainage through the thigh in Scarpa's triangle. Only 1 of the 7 patients died while still in the hospital. This case was secondary to perforation of a diverticulum of the descending colon. Of the other 6 patients, however, 3 died later of their primary disease: tuberculosis of the spine with meningitis (2 patients) and actinomycosis of the spine and the lungs (1 patient).

#### MORBIDITY AND MORTALITY RATES

Morbidity and mortality statistics in the 66 cases of perinephric abscess are compiled in tables 10 and 11. The long period of hospitalization necessary for these patients emphasizes the economic aspects of the disease. Surgical lesions which necessitate hospitalization for two months are relatively few.

The mortality rates associated with perinephric abscess should be interpreted in relation to the type of abscess. Among patients with simple perinephric abscess, for example, the mortality in this series was nil, if the 2 patients are excluded who died from causes other than the effects of the suppuration in the perinephrium. In complicated perinephric abscess, however, the mortality rate may be as high as 14 to 50 per cent. For the entire group, the mortality rate attributable to perinephric abscess was 15 per cent.

#### COMMENT

It is generally agreed that simple perinephric abscess is almost always secondary to infection elsewhere in the body. The primary focus may be trivial infection in the skin, the upper part of the respiratory passages or elsewhere. The path by which the perinephrium is infected, however, has been disputed.<sup>5</sup> In this connection, 25 cases of simple and multiple abscesses of one or both kidneys were reviewed. In these there was no evidence of perinephric abscess on postmortem examination. It should be pointed out, however, that tiny isolated abscesses in the perinephrium may be missed in routine autopsies.

Of the 2 patients with simple perinephric abscess with simultaneous involvement of the kidney on whom autopsy was performed, 1 showed no connection between the two lesions. In the other, the kidney appeared to have been involved from without. Two patients with complicated perinephric abscess, however, showed direct communication between the cortical and the perinephric abscesses through the true capsule of the kidney. It appears, then, that bacteria may reach the perinephrium

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5. Birdsall, J. C.: Perinephric Abscess, *J. Urol.* 25:405-412, 1931. Vermooten.<sup>3</sup> Mathé.<sup>1b</sup> Atcheson.<sup>1d</sup>

either by extension from abscesses in the kidney or directly from the blood stream. To be sure, bacteria are less apt to lodge in the poorly vascularized perinephrium than in the kidney with its excellent circulation. On the other hand, this very difference in vascularity favors growth and exhibition of virulence by bacteria which do happen to reach that region even if in small numbers.

Analysis of the data just recorded emphasizes the importance of attention to the history and the physical examination of patients with perinephric abscesses in order to arrive at an early diagnosis. Roentgenograms and laboratory data are only corroborative. Fixation of the kidney and the diaphragm has been emphasized by Mathé as an additional roentgen sign of perinephric abscess. When present, it indicates diffuse phlegmon and suppuration in the perinephrium or a localized abscess in the neighborhood of the upper pole of the kidney. Abscesses about the lower pole of the kidney, however, or anteriorly in the perinephrium, may not show this sign. In 1938, Menville<sup>6</sup> reported anterior displacement of the kidney by perinephric abscess. Here, again, abscesses situated anteriorly may not displace the kidney. Furthermore, great care must be taken in exposing true lateral films, for even slight departures from the true lateral may project the renal shadow far from its expected position so as falsely to suggest displacement of the kidney.

Although of minor importance in establishing a diagnosis of perinephric abscess, urinalysis may yield important data. It will be seen from table 8 that in cases of simple perinephric abscess the presence of albumin and white blood cells in the urine indicates gross involvement of the kidney itself by the suppurative process. Such data are thus useful in prognosticating morbidity (table 10).

The mischievous morbidity of perinephric abscess has been emphasized by many writers. Three factors promote the complications and delayed convalescence of the disease:

(a) Failure of Early Diagnosis: Perinephric abscess is usually so insidious that patients do not often present themselves early in the course of the disease. Instead, they appear after symptoms have progressed for days or months. Even after hospitalization, considerable time is often spent before a diagnosis is established. In this series of 66 patients, only 2 were operated on the day of admission. In an exceptional case, operation was not performed until one hundred and twenty-four days after hospitalization. The average delay was five and a half days.

Undue delay in the diagnosis and the drainage of perinephric abscess prolongs convalescence and increases the hazards of the disease because of extension of the lesion more and more widely through the perinephrium until neighboring structures are involved. Portal

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6. Menville, J. G.: The Lateral Pyelogram as a Diagnostic Aid in Perinephric Abscess, *J. A. M. A.* **111**:231-233 (July 18) 1938.

thrombophlebitis, intestinal fistulas, involvement of the iliopsoas bursa and extension into the pleural cavity through the diaphragm have occurred. Early drainage should prevent such complications. Sufficient delay, under observation, to permit localization of the inflammatory lesion, however, is undoubtedly beneficial. The duration of the delay must be guided by the clinical course of the patient and seldom needs to be more than two to five days. During this time, sulfathiazole 2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) may be administered. It is always advisable to delay surgical intervention as long as the patient continues to improve with chemotherapy and supportive treatment.

Perusal of hospital records often fails to reveal the cause for delay in diagnosis. Study of the progress notes, however, has indicated that the most common cause for delay is failure to consider the lesion as a possibility in the differential diagnosis. In some cases, the diagnosis is considered but then discarded because of the lack of gross physical findings or the presence of mobility in the palpable mass. It should be emphasized that physical signs may be minimal when the abscess has not penetrated the perinephric fascia of Gerota and that the palpable mass may be movable before the inflammation has extended through the paranephric fat.

The differential diagnosis in patients with obscure fever and particularly with pain in the loin should always include perinephric abscess with or without abscess of the kidney. Additional findings in the history and the physical examination serve to strengthen or weaken the impression.

(b) *Architecture of the Perinephrium*: The fibrofatty structure of the perinephrium with its many interlacing fibrous trabeculae favors neither prompt and complete localization of the inflammatory process nor rapid resolution following drainage. When the kidney itself is involved, its functional activity may play a role in delaying healing.<sup>7</sup> Finally, the relations of the perinephrium to the rib cage and the kidney sometimes make adequate drainage difficult to effect, and revision of wounds to facilitate drainage is therefore sometimes necessary.

(c) *General Condition of the Patient*: Patients ill because of complicated perinephric abscess are usually in poor general condition. The underlying disease has often been present for months or years, and the patients always show evidence of prolonged sepsis. Simple perinephric abscess is of relatively short duration, but the virulence and the toxicity associated with the infection in these cases are such as to

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7. The postoperative hospital stay of patients with perinephric abscess in whom there was no evidence of renal involvement was eight to sixty-one days (average, twenty-four); that of patients in whom the kidney was grossly involved was twenty-nine to one hundred and thirty-seven days (average, sixty-nine).

cause severe debilitation. Metabolic processes are disturbed; immunity is inhibited; wound healing is impaired, and convalescence is delayed.

Early diagnosis, adequate preoperative preparation, attention to technical details at operation and careful supportive postoperative treatment should decrease the morbidity and mortality rates of perinephric abscess to a minimum. Operative technic must be guided by the general principle of establishing and maintaining adequate drainage with the least possible trauma. Acid-cured tubes of gum rubber have been more serviceable than cigaret wicks. In 1941, Atcheson reported good effects from counterdrainage. This may prove useful in isolated instances.

Tight closure of the wound about the drain should be avoided. Wounds have been found to heal more quickly when bottlenecking is avoided. Meticulous care of the wound to avoid maceration and spread of infection is an exercise in surgical dressing. Postoperatively, the patient should be assured comfort, nutrition and hydration.

Exactly how far one should proceed at the time of the primary operation for incision and drainage of perinephric abscess is a disputed point. It is generally agreed that when nephrectomy is indicated, as in cases secondary to pyelonephritis or to renal calculi, it is best done at a second stage, at least two, and preferably more, weeks after the first operation. Whether or not nephrostomy should be done in these patients must be determined by the presence or absence of obstruction to the outflow of urine from the kidney. Careful judgment should be exercised in the question of the extent of exploration advisable in cases of simple perinephric abscess. It is best to do as little as is consistent with adequate drainage of the abscess at the first operation. It is important not to break the barriers within the perinephrium, which have localized the abscess, in an attempt to explore the entire kidney in search of lesions within it. A secondary operation for drainage of the kidney or for nephrectomy is far preferable to overzealous exploration at the first operation. However, patients must not be neglected after primary operations. Thus, 2 patients whose cases are recorded in table 11 who died as the end result of the complications of calculus disease of the kidney might possibly have had a different outcome had nephrectomy been done at the appropriate interval after the original operation.

The high mortality rate associated with complicated perinephric abscess deserves special mention. The fact that there is such a striking difference between the mortality rate with this type of abscess and that with simple perinephric abscess suggests that causes other than the perinephric abscess are responsible for the deaths. These causes have been listed in table 11. For purposes of prognosis, therefore, the nature of the underlying disease is of greater importance than the perinephric abscess itself.

## CONCLUSIONS

Perinephric abscess must be considered in the differential diagnosis of fever and pain in the loin or the flank.

The diagnosis is usually made by the history and the physical examination; roentgenograms and laboratory data are corroborative.

Fever, leukocytosis, elevated erythrocyte sedimentation rate and loin tenderness are almost constant findings.

The side affected, the sex incidence and the age incidence depend on the type of abscess.

Abnormalities in the urine indicate involvement of the kidney in the suppurative process.

The importance of adequate drainage of perinephric abscess with as little derangement as possible of the body defenses has been emphasized.

When nephrectomy is indicated, it is most safely done as a secondary operation.

Morbidity and mortality statistics are significant only when considered in relation to the type of abscess.

With simple perinephric abscess, the mortality rate is nil; with complicated perinephric abscess, it varies between 14 and 50 per cent.

# PROGRESS IN ORTHOPEDIC SURGERY FOR 1941

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE  
AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

## PREFACE

In the preparation of "Progress in Orthopedic Surgery for 1941" the titles of 2,397 articles of orthopedic interest were gathered from the *Quarterly Cumulative Index Medicus* for 1941. The number of articles reviewed in the final report is 824, or 34 per cent of the total. The editor of each section has selected the articles which he thinks have the greatest scientific interest and represent the most progress. The chairman of the editorial board has reviewed the material prepared for each section and has made certain additions and changes which seemed indicated to improve the publication as a whole.

On account of the war and the consequent added interest in fresh fractures and dislocations, it was thought advisable to publish the section dealing with this subject first. In addition there will be found throughout the publication many abstracts and references pertinent to military medicine. It is hoped that these will act as guides in improving the treatment of soldiers and sailors in the hospitals of our armed forces.

The style of every section is not uniform, and the number of editorial comments (which form so valuable a part of the publication) is not always the same. Both style and comments have again been left to the discretion of the editor of each section except for a few changes made by the chairman of the editorial board. Again we must state what was prefaced to the "Progress in Orthopedic Surgery for 1940":

. . . If the reader or the author of any article does not agree with the editorial comment, the editorial committee hopes that he will think of the remark as only one man's impression and as in no way representing the opinion of the entire editorial board.

It was thought advisable this year to appoint an assistant editorial board made up of members of the Academy. This was done, and the names of the members are listed accordingly.

The editorial committee wishes to express its appreciation to the group of physicians who although not members of the Academy have rendered valuable assistance to the editorial board in the preparation of the material for the different sections and to the editorial staff of the ARCHIVES OF SURGERY for its splendid cooperation in the publication of the material.

The members of the editorial board are as follows :

Dr. LeRoy C. Abbott, Dr. Walter P. Blount, Dr. Fremont A. Chandler, Dr. John R. Cobb, Dr. Paul C. Colonna, Dr. H. Earle Conwell, Dr. Frank D. Dickson, Dr. Rex L. Diveley, Dr. Ralph K. Ghormley, Dr. A. Bruce Gill, Dr. J. Hiram Kite, Dr. John G. Kuhns, Dr. Philip Lewin, Dr. I. William Nachlas, Dr. Winthrop M. Phelps, Dr. Robert D. Schrock, Dr. Alfred R. Shands Jr. (Chairman of the Editorial Board), Dr. Alan DeForest Smith, Dr. J. Spencer Speed, Dr. Arthur Steindler, Dr. Loring T. Swaim, Dr. J. Warren White and Dr. Philip D. Wilson.

The members of the assistant editorial board are as follows :

Dr. Lenox D. Baker, Dr. Frederic C. Bost, Dr. Keene O. Haldeman, Dr. Herman F. Johnson, Dr. D. H. O'Donoghue, Dr. R. Beverly Raney, Dr. Ralph Soto-Hall and Dr. Walter G. Stuck.

The following physicians acted as assistants to the editorial board :

For Dr. Abbott: Dr. John B. de C. M. Saunders, Dr. Carl Anderson and Dr. Edwin Schottstaedt; for Dr. Colonna: Dr. John T. Jacobs and Dr. A. L. Swenson; for Dr. Ghormley: Dr. H. Herman Young, Dr. Mark B. Coventry and Dr. Paul R. Lipscomb; for Dr. Schrock: Dr. Chester H. Waters, Jr.; for Dr. Shands: Dr. E. B. Dunlap, Dr. W. Richard Ferguson and Dr. C. M. Hanby; for Dr. Smith: orthopedic staff of the New York Orthopaedic Dispensary and Hospital; for Dr. Steindler: orthopedic staff of the Children's Hospital and the State University of Iowa College of Medicine; for Dr. Swaim: Dr. George J. Baer.

The editorial committee believes that the "Progress for 1940" has proved an acceptable addition to the orthopedic literature and hopes that this 1941 edition may also be a publication of great usefulness to those interested in the problems of orthopedic surgery.

(Signed) The Editorial Committee of the  
American Academy of Orthopaedic Surgeons.

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## I. FRESH FRACTURES AND DISLOCATIONS

*Fractures and Dislocations of the Head of the Humerus.*—Rendich and Poppel<sup>1</sup> have combined the results of clinical and dissecting room work to describe the unusual condition of posterior dislocation of the shoulder joint. They divide the condition into subacromial and subspinous types. It seems from their discussion that the dislocation is most commonly produced by forcible internal rotation of the shoulder causing a rupture of the posterior capsule. This happens most commonly in convulsive seizures, such as those of epilepsy. The authors indicate special diagnostic points but point out that a stereoscopic view of the shoulder shows the dislocation. A vertical view demonstrates the posterior displacement. They explain in some detail the findings which are suggestive of the condition on a single flat plate. [ED. NOTE: The diagnostic points on a flat plate seem to lose a great deal of importance when it is demonstrated by the authors that stereoscopic or vertical views permit immediate diagnosis.]

Moorhead<sup>2</sup> discusses fractures of the surgical neck of the humerus, dividing them into two types: those in which the apposition of the fragments is approximately 50 per cent or less and those in which there is no apposition. He says that the relation of the head of the humerus to the glenoid cavity is more important than that of the head to the shaft. He emphasizes the dangers of increasing the displacement by attempting to secure more perfect reduction. The treatment recommended is the use of a sling or one of its modifications with early active and passive motion to prevent adhesions about the shoulder joint. [ED. NOTE: This is a practical discussion of the treatment of a fracture which at times is difficult to reduce.]

Geckeler<sup>3</sup> reports 15 cases of fracture of the surgical neck of the humerus. He makes the comment that most of these fractures will heal under any form of treatment. He feels that formerly too much attention was paid to the anatomic reposition of the fragments and that not enough attention was given to the function of the arm; this resulted in adhesions and contracture following prolonged immobilization. He calls attention to the following observations of other authors recently reported in the literature: 1. The fragments will remain in relatively normal position after reduction provided the arm hangs at the side with

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1. Rendich, R. A., and Poppel, M. H.: Roentgen Diagnosis of Posterior Dislocation of the Shoulder, *Radiology* **36**:42-45 (Jan.) 1941.

2. Moorhead, J. J.: Conservative Treatment in Fractures of Neck of Humerus, *Connecticut M. J.* **5**:267 (April) 1941.

3. Geckeler, E. O.: Treatment of Fractures of Neck of Humerus Without Immobilization, *Surgery* **10**:917-926 (Dec.) 1941.



no support under the elbow (hanging traction). 2. The longitudinal muscles exert a squeezing effect on the fragments. 3. The tendon of the long head of the biceps brachii muscle controls the upper fragment, and the weight of the arm causes traction on this tendon. Geckeler's method of treatment is to place the arm in a sling and start active exercise immediately. In all 15 cases union was obtained in eight weeks. He recommends this method for all fractures of the neck of the humerus except those with which there is dislocation or decided displacement. [ED. NOTE: This is another modification of treatment by a hanging cast. The author reports excellent results with the use of only the weight of the arm for traction.]

*Fractures of the Shaft of the Humerus.*—Griswold, Hucherson and Strode<sup>4</sup> present the end results of treatment by a hanging cast in 305 cases of fracture of the humerus. Exceptions to the use of this method are listed as extension supracondylar fractures in children and extensive compound fractures which require early skeletal traction.

The principle of this form of treatment depends on traction exerted in the line of the humerus by the weight of the plaster cast extending from the knuckles to the axillary fold with the elbow at right angles. The cast is allowed to hang free on the sling around the neck; the sling is attached to a loop of wire incorporated in the cast at the wrist. When in bed, the patient should be kept in the Fowler position for the first week so that constant traction is maintained. Circumduction exercises of the shoulder are used from the beginning to minimize limitation of shoulder motions and muscular atrophy. Analysis of the group of cases reported shows an average age of 43.5 years and an average length of time of plaster fixation of forty-eight and eight-tenths days. The end results are highly satisfactory.

LaFerte and Nutter<sup>5</sup> have used the hanging plaster cast in 177 consecutive cases of fracture of the humerus. They consider this method of treatment suitable for all fractures of the humerus except those involving the condyles of the humerus or the supracondylar area of the humerus, comminuted fractures of the head and the neck with displacement and fractures of the greater tuberosity. They point out that lateral angulation can be corrected by a pad on the inner side of the elbow, medial angulation, by a sponge rubber pad in the axilla, and forward and backward angulation, by changing the height of the sling. They report no cases of delayed union or of nonunion. The average period spent in the cast was six weeks. [ED. NOTE: This method of treat-

4. Griswold, R. A.; Hucherson, D. C., and Strode, E. C.: *Fractures of Humerus Treated with Hanging Cast*, *South. M. J.* **34**:777-778 (July) 1941.

5. LaFerte, A. D., and Nutter, P. D.: *Treatment by Means of Hanging Plaster Casts in Fractures of the Humerus*, *Ann. Surg.* **114**:919-930 (Nov.) 1941.

ment has been universally accepted for fracture of the humeral shaft and in a few instances for fracture of the surgical neck as well as of the lower extremity of this bone. The fundamental principles of immobilization of the joints above and below the site of fracture are entirely disregarded in this method.]

Wright, Koenig and Shafiroff<sup>6</sup> review the various methods of treatment of fractures of the head and the shaft of the humerus and introduce a further modification of the hanging cast which they have termed the "extension-traction hanging cast." The plaster is applied with the patient in the sitting or the standing position with the arm freely suspended from the shoulder. It extends from the site of the fracture down to the wrist with the elbow in extension. Early motion of the shoulder and the wrist is encouraged. It is claimed that faulty position and alinement are corrected by the method itself, although reduction without anesthesia is attempted at the time of application of the plaster. Twenty-two cases are reported, and in 90 per cent of these abduction was completely restored within two months after fracture. Absence of pain was a constant feature in every case. [ED. NOTE: The high percentage of good end results obtained by the authors further substantiates the efficacy of this popular method of treating fractures of this type. This modification seems particularly desirable for fractures of the neck of the humerus and the upper third of the shaft but not for fractures in the middle and lower thirds. The average age period of the patients treated is not given, but it is assumed that they were a group of young vigorous servicemen.]

In a discussion of 35 cases of fracture of the humerus, Eve and Daniel<sup>7</sup> emphasize the merits of the Gurd type of spica cast for the shoulder. The authors compare the Gurd cast with the simpler hanging cast and state that they favor the former. They used local anesthesia in reducing most of the fractures. There were no nonunions, and in all cases good functional results were obtained. [ED. NOTE: Gurd<sup>8</sup> has developed a special axillary pad to support the arm over which a molded plaster cast is applied. This produces excellent results as the series of Eve and Daniel indicates. Recent experience with the less cumbersome hanging cast has convinced many orthopedic surgeons of its efficiency and comfort. Either method is less strenuous for the patient than the usual abduction splints and casts.]

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6. Wright, A. M.; Koenig, G. A., and Shafiroff, B.: Extension Hanging Cast for Fractures of Humerus, *Mil. Surgeon* **88**:542-545 (May) 1941.

7. Eve, D., and Daniel, R. A., Jr.: Treatment of Fractures of Shaft of Humerus, *South. M. J.* **34**:311-315 (March) 1941.

8. Gurd, F. B.: Simple Effective Method of Treatment of Fractures of Upper Two-Thirds of Humerus, *Am. J. Surg.* **47**:443-453 (Feb.) 1940.

*Fractures of the Elbow.*—Shorbe<sup>9</sup> has collected 32 cases of traffic elbow (car door arm or sideswipe elbow), or injury caused by riding with the elbow resting on the window of a car. He points out the extreme comminution occurring in the humerus, the radius, the ulna or all three. In analyzing the end results he notes that in 8, or 25 per cent, of 32 cases an entirely useless arm resulted.

Wood<sup>10</sup> reports that approximately 6 patients with this condition are treated each year at the Louisville City Hospital, Louisville, Ky. An estimated 50 per cent of these require amputation, and the others show variable degrees of permanent deformity or dysfunction. The writer emphasizes that this severe crippling injury is easily avoidable and should never occur.

Trynin<sup>11</sup> reports the use of a carpenter's clamp in a case of intercondylar T-shaped fracture of the lower end of the humerus with marked displacement of the fragments. The elbow was manipulated under local anesthesia, and the point was placed in acute flexion. Check-up roentgenograms disclosed that the metaphysial portion of the lower fragment was displaced medially on the shaft. To correct this a carpenter's clamp was applied over felt pads at the region of the epicondyles, and by gradually tightening this the fragments were slowly approximated. After several days roentgen examination disclosed almost complete apposition of the fragments. This was maintained by leaving the clamp in place for four weeks. Five months after the injury extension to 170 degrees and flexion to 45 degrees were possible. Roentgen examination at that time disclosed firm union with good alinement of the fragments.

O'Ferrall<sup>12</sup> discusses the various types of fracture of the radial head. He indicates that he prefers conservative treatment of impacted fractures of the head or fractures without displacement. He emphasizes, however, that it is important that immobilization should be carried out in the position of flexion of the elbow and supination of the forearm and that this position should be protected for three or four weeks. For the more severe types he recommends open operation. If there is a small fragment broken loose, it can be removed, leaving the remainder of the head. In the treatment of other types all the fragments can be removed; the neck can be carefully rounded off, and the orbicular ligament can be repaired. He stresses the importance of complete

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9. Shorbe, H. B.: Car Window Elbows, *South. M. J.* **34**:372-376 (April) 1941.

10. Wood, C. F.: Traffic Elbow, *Kentucky M. J.* **39**:78-81 (Feb.) 1941.

11. Trynin, A. H.: Intercondylar T Fracture of Elbow, *J. Bone & Joint Surg.* **23**:709-711 (July) 1941.

12. O'Ferrall, J. T.: Fractures of the Head of the Radius, *New Orleans M. & S. J.* **93**:367-370 (Jan.) 1941.

hemostasis before closure. He recommends again the same position of flexion and supination. In any case he feels that early physical therapy is important; however, there should be careful avoidance of forced passive motion.

*Fractures of Both Bones of the Forearm.*—Thorndike and Dimmler<sup>13</sup> report 364 cases of fractures of the radius and ulna in children. In 200 of the cases the fracture was in the distal third of the forearm; in 58 it was in the proximal third, and in 106 it included the head of the radius and the olecranon process. The authors note that growth abnormalities are caused by disturbance of the proliferating cells of the cartilaginous plate and that epiphyseal separation does not necessarily injure these cells or interfere with their function. For this reason growth disturbance is not common following ordinary epiphyseal separation. In 50 per cent of the cases the fracture of the distal part of the forearm was of the greenstick type; in these cases closed reduction with a molded short arm cast or a sugar tong splint was done. The authors mention that long arm splints or casts should be used for fractures in the upper third of the forearm. In considering fractures of the radial head, they recommend closed reduction and fixation in acute flexion with adhesive tape and open reduction only if complication arises. The incidence of open reduction was remarkably low, being 1 per cent in cases of fracture of the distal third of the forearm, 0 per cent in cases of fracture of the proximal third of the forearm and 6 per cent in fractures of the elbow.

In recent years at the Orthopedic Hospital in Copenhagen, Denmark, Sorensen<sup>14</sup> has used with success a method of traction with a water pail for reduction and immobilization of fractures of the forearm. The fracture is anesthetized with local anesthetic. The hand is painted with mastisol (a solution of mastic in benzene) and fixed by adhesive tape around the fingers to two metal plates; these are screwed to a perforated cross bar, which is hung on a pulley above the head of the patient. The traction is exerted downward by a water pail hung on a sling above and close to the elbow. The upper arm is placed in 90 degrees of abduction; the elbow is placed at 90 degrees of flexion, and the forearm and the hand are placed perpendicular, midway between pronation and supination. By gradually filling the pail with water, the traction can then be regulated and eventually is combined with manual reduction until palpation and roentgenograms show that the fracture is reduced. A plaster cast is then applied. The traction is gradually reduced, and the apparatus is

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13. Thorndike, A., Jr., and Dimmler, C. L., Jr.: Fractures of Forearm and Elbow in Children: Analysis of Three Hundred and Sixty-Four Consecutive Cases, *New England J. Med.* **225**:475-480 (Sept. 25) 1941.

14. Sorensen, F.: The Water Pail Traction Method in Reposition and Bandaging of Forearm Fractures, *Ugesk. f. læger* **103**:269-270 (Feb. 27) 1941.

unmounted. Even severe overriding can be corrected. Reduction and immobilization can thus be accomplished at one time. [ED. NOTE: This method was previously described by Phillippides<sup>15</sup> in 1937.]

*Colles Fracture.*—Hanflig<sup>16</sup> describes a rather ingenious apparatus with which to maintain the reduction of a Colles fracture while the cast is being applied. The apparatus is not for reduction of the fracture. Essentially it consists of a central post with a rest on which the palmar surface of the wrist is supported and an appliance through which traction can be applied to the fingers with Japanese finger traps. Proper adjustment can be made to fit any degree of flexion or ulnar deviation deemed advisable. Hanflig also states that with this apparatus the anesthetic time can be shortened since the anesthetic can be stopped when the arm is first placed in the apparatus. The apparatus likewise obviates the need of assistance. [ED. NOTE: It appears that this apparatus answers the purpose for which it was fashioned, but the necessity of it is questionable. From the cuts presented it seems that the cast must be applied with the elbow in complete extension and the forearm in complete supination.]

*Fractures and Dislocations of the Carpus and the Hand.*—Schafer<sup>17</sup> reports a case of bilateral semilunar luxation with simultaneous unilateral fracture of the scaphoid bone as proved by roentgen examination. The patient was a vaudeville artist 31 years of age and a member of a bicycle performing act. He had fallen from a platform 5 meters high when one of the wires holding the platform broke while he was in the act of standing on his hands, and he was thrown to the floor. The luxations were easily reduced by hyperextension of the wrists. But while this was being done, slight torsion of the left scaphoid proximal fragment occurred. Fixation was in plaster casts. After a few days the patient complained of severe pain in the left hand, and an attempt was made while he was under anesthesia to improve the position of the displaced scaphoid fragment. Reduction was not possible. On the contrary, the displacement was exaggerated. After three weeks the plaster cast was removed from the right hand, and after-treatment was begun. After the cast was removed from the left hand, it was found that not the slightest movement was possible in the wrist. For this reason the scaphoid fragment was surgically removed under local anesthesia. The wrist was then movable. Fixation was accomplished in plaster. Three

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15. Phillippides, D.: Reduction of Fractures by Traction, *Chirurg.* **9**:409-418 (June 1) 1937.

16. Hanflig, S. S.: Apparatus to Facilitate Treatment of Colles' Fractures, *Am. J. Surg.* **52**:386-389 (May) 1941.

17. Schafer, A.: Bilateral Perilunar Luxation with Simultaneous Unilateral Fracture of Scaphoid Bone, *Arch. f. orthop. u. Unfall-Chir.* **40**:405-411, 1940.

weeks later the plaster cast was removed also from the left hand. After careful exercises the patient was able to resume the pursuance of his vocation. It is emphasized that the good results in this case were no doubt aided by the fact that the man was young, that he knew he could expect no compensation and, finally, that he was possessed of most unusual will power.

Cave<sup>18</sup> analyzes the cases of fracture at the Massachusetts General Hospital, Boston, and determines that retrolunar dislocation of the capitate bone with fracture or subluxation of the navicular bone was the third most common carpal injury in these cases. He ascribes the mechanism of the fracture and the dislocation to forced dorsiflexion of the wrist, usually caused by a fall on the outstretched hand. This results in a forcible tearing between the lunate and capitate bones with a dorsal dislocation of the capitate bone, the lunate bone maintaining its normal relation to the radius. The same force must either dislocate or fracture the navicular bone. Cave points out the importance of distinguishing accurately between this condition and simple dislocation of the lunate bone, the important point being the maintenance of normal relation between the lunate bone and the radius, while the capitate bone is displaced dorsally and the navicular is rotated or fractured. He indicates that the proper treatment in any case is early manipulation and that if it is carried out early enough it may be successful. If there is a fracture of the navicular bone and if the fragments are not accurately replaced by the closed reduction, open operation should be done and a dowel graft placed between the fragments at once, without waiting to determine whether or not union will occur. In cases in which closed manipulation does not satisfactorily reduce the dislocation, open operation becomes necessary, and it in itself may fail. The author emphasizes the importance in open operation of two separate incisions to expose the capitate and navicular bones. The dorsal incision is for the purpose of exposing the capitate bone and reducing the dislocation, and a curved radial incision is for the purpose of exposing the navicular bone to carry out the reposition and the dowel grafting. If closed manipulation and open operation both fail to restore anatomic position, further operation is indicated, leaving two procedures, namely, removal of both the lunate and the navicular bones or wrist fusion. Cave discusses briefly the ultimate value of these two procedures. There are several excellent case reports with excellent roentgen and anatomic drawings. [ED. NOTE: This is a good article with an accurate description and a clear recommendation as to treatment.]

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18. Cave, E. F.: Retrolunar Dislocation of Capitate with Fracture or Subluxation of Navicular Bone, *J. Bone & Joint Surg.* 23:830-840 (Oct.) 1941.

Soto-Hall and Haldeman<sup>19</sup> review the cases of 50 patients with various types of fractures of the carpal scaphoid bone and evaluate the various operative measures which have been employed in the treatment of nonunion.

The preponderance of male patients (47 to 3) indicates that the lesion is essentially an industrial injury. The majority of cases occur in the third and fourth decades of life. The high incidence of fractures to the waist of the bone and the high percentage seen early allow the writers to stress a conservative and uniform plan of treatment. The most frequent associated injury was dislocation of the lunate bone; it was present in 6 of the 50 cases, while fractures of the lower end of the radius occurred in 3.

Success of treatment depends on the recognition of the fracture within two or three weeks of the injury and on adequate and prolonged immobilization. Treatment of the various types should be considered. These types include: (1) lesions of the body through the waist; (2) lesions through the proximal pole; (3) lesions of the tubercle, and (4) comminuted fractures. In types 1 and 2 immobilization should consist of a plaster cast holding the wrist in full radial flexion and 30 degrees dorsiflexion, including the thumb, which is held in full abduction and extension. The abduction of the thumb should be maintained by pressure on its base rather than on its tip because of the possibility of subluxation of the metacarpophalangeal joint of this digit. Immobilization of the wrist is continued for ten to twelve weeks, depending on the roentgen appearance. A reenforced leather wristlet support may then be used for more prolonged immobilization. Fractures of the tubercle usually heal in from four to six weeks, and the thumb need not be included. In cases of comminuted fractures excision of the fragments should be done early, if there is indication for it, to avoid arthritic changes.

In cases of nonunion the operation of drilling recommended by Schnek has limited value and should be combined with excision of the interposed fibrous tissue and the insertion of a bone graft peg from the lower end of the radius. This additional procedure definitely improves the chances of union. Evidence of aseptic necrosis of the proximal fragment does not necessarily indicate that excision should be performed, for the authors have seen revascularization and osseous union of such a fragment following bone grafting.

Analysis of end results in 21 cases of recent fractures treated conservatively showed osseous unions in 20. In 4 cases of old ununited fractures treated conservatively there were no unions. Among 10

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19. Soto-Hall, R., and Haldeman, K. O.: Conservative and Operative Treatment of Fractures of the Carpal Scapoid, *J. Bone & Joint Surg.* **23**:841-850 (Oct.) 1941.

cases in which drilling alone was done, union took place in 5. In 8 cases in which treatment consisted in combined bone grafting and drilling, osseous union occurred in 6. Of the 50 patients, 36 returned to their former type of work.

Pathologic study of 5 excised navicular bones showed a characteristic fusiform area of absorption occurring along the line of fracture which was replaced by fibrous connective tissue. Near the center of the fracture this gives an appearance of cystic degeneration, although a true cyst does not occur. Microscopic studies of the articulating cartilage show the inability of hyaline cartilage to regenerate, the defect being filled in with connective tissue which may take on some of the characteristics of fibrocartilage.

Lamb,<sup>20</sup> in a detailed discussion of fractures of the fingers, stresses the accompanying injury to the tendons and the tendon sheaths with the usual result of permanent disability. He states also that in compensation estimates the value of fingers is definitely underrated. The usual estimates provide for no adequate remuneration to the person for the loss of the use of a digit. In many instances in which poor results are obtained, the person would prefer to have the finger amputated to having the disability of a stiff finger.

The surgical anatomy of the fingers, the classification of the various fractures and the methods of reduction are covered in an elementary manner, beginning with fractures of the proximal phalanx, which are more liable to angulate and override than those of the middle phalanx, and ending with those of the spongy portion of the distal phalanx. There is always the possibility of partial or complete severance of tendons in compound fractures.

The various methods of reduction and immobilization presented are standard types, varying from the use of a simple palmar ball or roller bandage in the curve of the fingers to the use of the banjo splint, which is particularly applicable to multiple fractures. Lamb stresses the importance of prevention of pressure necrosis caused by improperly applied splints.

In postoperative care early active motion with light massage is recommended. Too much importance cannot be placed on massage and the wholehearted cooperation of the patient in regaining function.

Kaplan<sup>21</sup> gives an excellent review of the diagnosis, the prognosis and the treatment of fractures of the hand. He emphasizes particularly the fact that long immobilization tends to lead to diminished circulation.

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20. Lamb, E. D.: Fractures of the Fingers, *Journal-Lancet* **61**:372-374 (Sept.) 1941.

21. Kaplan, L.: Treatment of Fractures and Dislocations of Hand and Fingers: Technic of Unpadded Casts for Carpal, Metacarpal and Phalangeal Fractures. *S. Clin. North America* **20**:1695-1720 (Dec.) 1940.



muscle and bone atrophy and stiff joints. Active motion should be instituted early, provided proper immobilization can be maintained. For fractures of the navicular bone, he uses an unpadded plaster cast which extends from the elbow to the middle of the hand and out to the last joint of the thumb. If union does not result after several months, drilling may be employed. In cases of dislocation of the entire carpus, he emphasizes the importance of the accompanying fracture of the radius and the ulna, which usually occurs at the articular surface, and recommends the use of an unpadded cast with mobilization after six weeks. In discussing Bennett's fracture, he advises waiting three to four days before manipulation is carried out, and if the position cannot be readily held, he suggests fixed wire traction through an unpadded cast. In treating fractures of metacarpals with displacement, he again recommends waiting a few days before manipulation is carried out. He notes that it is particularly important in treating phalanges that adequate motion be permitted in the uninvolved portions of the finger and in the uninvolved fingers in order to prevent residual stiffness. [ED. NOTE: Too little attention is given to the proper care of fractures of the bones of the fingers, the hand and the wrist. The days lost from work from such injuries is too high. More attention should be directed to such disabilities.]

Spotoft<sup>22</sup> states that as ordinarily practiced pulp extension for fractures of the fingers has several disadvantages which can be eliminated by the use of a cannula. A suitable cannula is inserted through the pulp at the usual site, and the tip of the cannula is broken off. A fine metal wire is then drawn through the cannula, and the rest of the procedure is as usual. The cannula should be short, heavy and polished. An ordinary WR cannula is sufficient. The tip of the cannula should be toward the side on which it will not interfere with the other fingers (or toes). Small pledgets of gauze soaked in mastisol are placed over the puncture wounds on both sides of the pulp to prevent infection. Extension by this method is painless, even with considerable traction. The cannula does not cut into the pulp like a wire does, and infection of the puncture canal is thus prevented. If the wire breaks, another can easily be inserted.

*Fractures of the Head and the Neck of the Femur.*—A thorough study of the problem of fractures of the hip has been made by the Fracture Committee of the American Academy of Orthopaedic Surgeons.<sup>23</sup> It is based on a careful analysis of 1,485 cases submitted by

22. Spotoft, J.: Cannula Extension for Fractures of the Fingers, *Ugesk. f. læger* **102**:627-628 (June 13) 1940.

23. Treatment of Fractures of Neck of Femur by Internal Fixation, Report of Fracture Committee of American Academy of Orthopaedic Surgeons, *J. Bone & Joint Surg.* **23**:386-390 (April) 1941.

a large number of surgeons. Rigid requirements as to site of fracture, evidence of displacement, reduction and follow-up observation preclude the possibility of confusion with simpler intertrochanteric or impacted fractures.

Of 241 cases analyzed in detail, union was found to occur in 70.1 per cent. There was a mortality rate in the entire series of 11.6 per cent. Severe arthritic changes in the hip joint occurred in 14 per cent.

[ED. NOTE: The committee is continuing its work and will study the late effects of internal fixation on the fracture of the head of the femur and the hip joint. Its opinions are based on the most severe requirements. This report is of immense scientific value.]

Boyd<sup>24</sup> reviews 150 fractures in the neck of the femur treated at the Willis C. Campbell Clinic, Memphis, Tenn., and sets forth general rules of treatment. With improved technic and local anesthesia when necessary almost any patient with such a fracture can be operated on, and a flanged nail can be inserted. Operations are performed as soon as possible to prevent discomfort and unfavorable complications. A flanged nail can be placed under roentgen guidance with a minimum of shock. After operation the patient is moved about freely in bed and wheel chair. No weight bearing is allowed for several months. Seventy-five per cent of the patients were female; more than one third of them were in the seventh decade of life. There was a mortality rate of 10.2 per cent and in 86 per cent of those patients that could be followed bony union was obtained. [ED. NOTE: The author's salient observations on early operation and freedom from weight bearing after operation are most important. Many failures in the early days of hip nailing resulted from allowing patients to bear weight too early. It was overlooked that the cancellous atrophic bone in the femoral head provided only nominal grasp on the nail in spite of the roentgen appearance of rigidity. We feel that the patient should be allowed out of bed early in a wheel chair but that no weight bearing should be permitted for several months. One main advantage of doing open reduction and internal fixation of the hip, especially in treating aged patients, is that the patient can be allowed out of bed, and this prevents serious complications, especially pneumonia.]

Geckeler and Tuttle<sup>25</sup> report the use of parallel metal screws (Martin method) in 50 cases of fracture of the neck of the femur since October 1936. Fractures are reduced, and the position is checked by fluoroscopic examination. Guides and drills also are placed with the use of the fluoroscope.

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24. Boyd, H. B.: Treatment of Acute Fractures of the Neck of the Femur, *South. Surgeon* **10**:364-371 (May) 1941.

25. Geckeler, E. O., and Tuttle, A.: Fractures in Neck of Femur, Accurate Subcutaneous Fixation with Screws, *Surg., Gynec. & Obst.* **72**:106-111 (Jan.) 1941.

The authors use steel screws, which they state do not result in bone absorption owing to the tightness with which they are fixed in the bone.

[ED. NOTE: The illustrations show good placing of the screws and excellent reductions. This probably is the explanation of the tightness of the fixation and the reason why there is little absorption of bone. With good reduction and adequate fixation most of the common unfavorable complications are eliminated. Much aseptic necrosis or extrusion of the nail is due to poor reduction at first and inadequate fixation. These complications are becoming less frequent as surgeons are devising better ways to reduce and anchor these fractures.]

After a discussion of the hip joint from the anatomic and the physiologic points of view, Engel<sup>26</sup> presents his methods of treating various types of fracture in this joint.

For some irreducible central dislocations of the head of the femur he uses a rather formidable operation in which the medial side of the acetabulum is exposed and is forced back into its normal position.

For treatment of fractures in the neck of the femur he describes the technic of blind nailing with the aid of the well known Engel-May direction finder. The same technic is used in treating some intertrochanteric fractures in which the trochanteric fragment is large enough to hold a Smith-Petersen nail without splitting.

[ED. NOTE: Exception may be taken to the observation that the Smith-Petersen nail becomes surrounded by a "fibro-cartilaginous membrane" which "seems to give off blood vessels" into the head and the neck of the femur. Could this not be fibrosis about the nail caused by electrolytic irritation from the metal in the nail?]

Eyre-Brook and Pridie<sup>27</sup> report 75 consecutive cases of intracapsular fractures of the femur in which a Smith-Petersen nail was used. In the presentation of their series of cases there is a rather interesting analysis of end results: In 58 per cent bony union was obtained; in 13 per cent fibrous union; in 10 per cent doubtful union; in 8 per cent the pinning failed; in 6 per cent necrosis of the femoral head developed, and in 4 per cent there was infection with resultant nonunion. In analyzing the cases of necrosis of the femoral head, the authors bring out the point that there was a remarkably higher percentage of necrosis in the younger age groups. The age distribution was as follows: under 30 years, 60 per cent; between 30 and 60 years, 16 per cent, and between 60 and 90 years, 12 per cent. The authors point out that this is of considerable significance from the standpoint of prognosis. The mortality rate in this series was 5.3 per cent.

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26. Engel, G. C.: Fractures About the Hip, *S. Clin. North America* **20**:1721-1741 (Dec.) 1940.

27. Eyre-Brook, A. L., and Pridie, K. H.: Intracapsular Fractures of Neck of Femur: Final Results of Seventy-Five Consecutive Cases Treated by Closed Method of Pinning, *Brit. J. Surg.* **29**:115-138 (July) 1941.

Sandner and Thompson<sup>28</sup> list the different varieties of fractures of the femoral neck and discuss the anatomic features of the region in question and the changes occurring in old age which lead to the prevalence of this fracture.

The mechanism causing this fracture is discussed in considerable detail. The force causing the injury may act in at least one of three primary directions. When the force acts in the lateromedial direction, as in a fall on the greater trochanter, the compression element tends to produce an impacted fracture of the neck or a central dislocation of the head of the femur. When the force acts in an anteroposterior direction resulting in a rotation mechanism, various types of fractures of the femoral neck occur. With the force acting vertically from above downward directly on the head of the femur, as the force caused by a misstep, the shearing mechanism is the major factor with a decrease of the neck-shaft angle to less than 135 degrees.

[ED. NOTE: The authors discuss and consider at length the mechanical aspects of this fracture, the details of which have been painstakingly worked out.]

Wise<sup>29</sup> gives a detailed description of the gross pathologic and the histologic study of a specimen in which a transcervical fracture of the femur occurred thirteen months before death. A vitallium Smith-Petersen nail was used to transfix the fragments. Grossly, there was evidence of solid bony union with the fracture site faintly visible. The articulating cartilage of the head and the ligamentous attachments of the greater and lesser trochanters were dark brown. This was thought to be due to degeneration, although the cartilage was smooth, normal in thickness and well preserved. By special stain this pigment was found to be iron.

The outstanding feature was the glistening smooth surface of gray membrane which lined the nail tract throughout its entire course. Microscopic study of this lining showed it to consist of two well defined layers, viz., an inner layer of connective tissue and an outer layer of bone trabeculae. Numerous blood vessels were present in the outer section of the connective tissue layer in addition to groups of small deeply stained pigmented granules of iron. These pigment granules are known as rust granulomas. Since in this instance a vitallium nail, in which there is no iron, was used, they were considered to be derived from broken-down red blood cells. The new blood vessels in the connective tissue of the nail tract apparently increase the blood supply across the fracture site with better nutrition of the head. Massive bone

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28. Sandner, E., and Thompson, E. C.: Causation of Fractures of Neck of Femur, *M. J. Australia* 2:383-391 (Oct. 4) 1941.

29. Wise, R. A.: Histologic Study of Transcervical Fracture of Femur after Internal Fixation, *J. Bone & Joint Surg.* 23:941-947 (Oct.) 1941.

lamellas along the nail tract indicate that this alloy does not prevent bone formation. The tract made by the nail produces a fibrous tissue cavity not unlike a bone cyst.

*Radiation Fractures of the Neck of the Femur.*—In a comprehensive study Strauss and McGoldrick<sup>30</sup> point out that the occurrence of fractures of the femoral neck as a complication of irradiation for malignant growth in the pelvis is not infrequent. Their study gives a review of the anatomic and physiologic considerations, a discussion of causes other than radiation of spontaneous fracture (e. g. nutritional defect and metastasis), a consideration of radiation therapy as it affects adult bone and a survey of reported cases. They add 4 of their own cases. This study shows conclusively that spontaneous fractures of the neck of the femur with pathologic findings at autopsy characteristic of radiation effects should have serious consideration. It must be borne in mind that the vascular supply of the femoral neck is terminal and vulnerable to postradiation vascular occlusion. Owing to the proximity of the femur to the surface the depth dose to the bone and its vascular supply is practically the same as the surface dose. This must be borne in mind in evaluating the term "relative radiation resistance." Excessive roentgen therapy, whether given in one prolonged cycle or in smaller repeated cycles, imperceptibly reaches dangerous proportions, the consequences of which become more serious with the lapse of time. In addition, these patients at the onset are poorly nourished owing to calcium-phosphorus imbalance and therefore are more susceptible to fractures. [ED. NOTE: The authors' suggestion relative to the prevention of this disabling complication by giving greater protection to this vulnerable area is most appropriate and should be followed by roentgenologists.]

Hight<sup>31</sup> reports a spontaneous fracture of the femoral neck of a man 58 years of age following roentgen therapy for a malignant growth of the penis with involvement of the inguinal glands.

A review of 1,084 cases with primary malignant growth in the region of the pelvis treated by roentgen therapy in the Pondville Hospital at Norfolk, Wrentham, Mass., discloses only 1 case of this type, giving an incidence of 0.09 per cent. This occurred without any evidence of metastasis to the neck or the head of the femur, but there was contributing arteriosclerosis. In other clinics the average incidence has been approximately 2.5 per cent.

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30. Strauss, H., and McGoldrick, J. L.: Fractures of Femoral Neck Following Roentgen Therapy for Gynecologic Malignancy, *Am. J. Obst. & Gynec.* **41**:915-934 (June) 1941.

31. Hight, D.: Spontaneous Fracture of Neck of Femur Following Roentgen Ray Therapy over Pelvis, *J. Bone & Joint Surg.* **23**:676-681 (July) 1941.

It is emphasized that in giving roentgen therapy over the pelvis, the portals should be so placed as not to include the region of the femoral necks.

Baker<sup>32</sup> gives a report of a case in which a fracture appeared gradually in the neck of the femur following roentgen therapy for uterine carcinoma. [ED. NOTE: The development of the deformity in this case resembled the changes seen in cases of slipped femoral epiphysis. Since there was no evidence of skeletal metastasis as the cause of the fracture, it appears that radiation osteitis was the cause. Perhaps roentgen therapy to pelvic viscera produces marked alterations in the blood supply of the adjacent tissues with ischemia of the neck of the femur.]

*Fracture-Dislocations of the Hip.*—King and Richards<sup>33</sup> review the history and the mechanism of injury in fracture-dislocations of the hip, which are characteristically an automobile injury. Their study includes experimental lesions of this type in a series of 8 dogs and a report of 7 clinical cases. The experimental work demonstrates that rapid disintegration occurs in the hip joint following incomplete reduction; in each case a severe degree of degenerative arthritis developed within a few weeks.

The three common varieties are: (1) fracture of the posterior lip of the acetabulum; (2) sprain fracture of the femoral head, in which a small fragment of the head attached to the round ligament remains in the acetabulum, and (3) transverse fracture across the floor of the acetabulum.

The indications for open reduction are: (1) largeness of the lip fragment of the acetabulum and failure to return to normal position when the head is reduced; (2) presence of the lip fragment in the acetabulum; (3) impossibility of the head being perfectly reduced or a fragment of it being free in the acetabulum; (4) fracture through the floor of the acetabulum allowing rotation of the distal half of the innominate bone, and (5) associated fracture of the femoral shaft preventing control of the head.

The operative technic is described in detail, the approach consisting of an incision from the posterior iliac spine outward and downward to the base of the greater trochanter. As the two halves of the gluteus maximus muscle are retracted from each other, there is complete exposure of the sciatic nerve, the gluteus medius, the piriformis, the obturator internus and the gemelli muscles. With the sectioning of

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32. Baker, L. D.: Spontaneous Fracture of Femoral Neck Following Irradiation, *J. Bone & Joint Surg.* **23**:354-358 (April) 1941.

33. King, D., and Richards, V.: Fracture-Dislocations of the Hip Joint, *J. Bone & Joint Surg.* **23**:533-551 (July) 1941.

the common tendon of the latter three muscles the posterior wall of the acetabulum is easily exposed. After the lip fragment of the acetabulum is replaced, it is held in place with one of the commonly used bone screws, which should be directed at an oblique angle upward to avoid penetrating the articulating cartilage. Immobilization for eight to ten weeks following the operation is recommended, with weight bearing at the end of twelve weeks.

A detailed case analysis is not given, although a series of roentgenograms of 3 patients in whom accurate replacement of the lip fragment was done show clear-appearing hip joints at the end of three and five years.

Roentgenograms of hips in which there was inaccurate replacement compared with those showing perfect position well illustrate the complicating arthritis demonstrated in the experimental study.

[ED. NOTE: This excellent article illustrates the importance of accurate replacement of fragments involving articulating surfaces, particularly in weight-bearing joints.]

*Trochanteric Fractures of the Femur.*—Lippmann<sup>34</sup> discusses the use of the corkscrew bolt for internal fixation of intertrochanteric fractures of the femur. He points out that with intertrochanteric fractures there is a tendency for separation of the fragments and return to a varus position following reduction. He further points out that any method of traction will prevent this but that fixation and rest in bed of long standing for elderly people carries a high mortality rate. He feels that open operation is not justified for young healthy patients, but that it is necessary for elderly people who will not stand confinement. He further states that this corkscrew causes direct traction between the head and the shaft fragment, adequately maintaining the position. He reports 3 cases in which it was used, all of them being cases of simple trochanteric fractures without comminution. [ED. NOTE: Use of this bolt seems to have the same contraindication in cases of intertrochanteric fractures as does the Smith-Petersen nail or its modifications, namely, that the results are satisfactory only if there is no comminution and there is a long intact fragment of the trochanter firmly adherent to the shaft. In the presence of comminution, internal fixation requires some method of fixation of the bolt through the shaft of the femur distal to the fracture line. For this reason we do not believe this bolt would work in the ordinary comminuted intertrochanteric fracture.]

Morris<sup>35</sup> discusses a group of trochanteric fractures and emphasizes again the unusually high mortality rate associated with this type of

34. Lippmann, R. K.: Role of Internal Fixation with Corkscrew Bolt in Intertrochanteric Fractures, *J. Mt. Sinai Hosp.* 7:459-466 (Jan.-Feb.) 1941.

35. Morris, H. D.: Trochanteric Fractures, *South. M. J.* 34:571-578 (June) 1941.

fracture in the average charity institution. He discusses the various types of internal fixation and the requirement for each, observing that he feels the best results occur with the Neufeld nail or with the Smith-Petersen nail and the Thornton plate. The latter was used in a series of 28 cases which he reports. In this series he was able to reduce the mortality rate to 21.4 per cent by internal fixation. He concludes that internal fixation "adds greatly to the comfort of the patient, reduces pain, facilitates nursing care and definitely reduces the length of hospitalization." [ED. NOTE: This article again calls attention to the fact that it is the patients who are poor operative risks who most require operative reduction, since the healthy patient will usually recover by almost any recognized method of treatment.]

*Fractures of the Shaft of the Femur.*—Lewis<sup>36</sup> gives a report of the treatment of 156 fractures of the femur with Russell or balanced traction. He describes an unfortunate experience with skeletal traction in which infection of the bone occurred around the knee, and he is apparently convinced that this is an unsatisfactory method for treatment of fractures of the femur. The mortality rate was only 3.2 per cent, although the average age in this series was 58 years. The average days of hospitalization were one hundred. The author reports 7 cases, or about 3.5 per cent, in which reduction could not be obtained. In 5 of these open reduction with internal fixation was done, and satisfactory results were obtained. He tabulates the results obtained in those patients treated throughout by Russell traction; he had 100 per cent good results in those with shaft fractures and over 90 per cent good results in those with intertrochanteric fractures. The figure for patients with shaft fractures does not include the 7 cases which the results were unsatisfactory; in these Russell traction had been discontinued. The author stresses the importance of close attention to the detail of application of Russell traction apparatus. [ED. NOTE: This author presents an enthusiastic argument for the use of Russell traction. His series of cases shows results far superior to those reported by other writers using similar methods of treatment. He reports no delayed union and no nonunion in this series of 71 fractures of the shaft. The mortality rate for the series of 3.2 per cent, including a large number of old people, is remarkably low. The author's condemnation of skeletal traction appears to be based largely on the use of tongs and Steinmann pins, although he does mention Kirschner wires; apparently skeletal traction was used in conjunction with a Thomas splint with a Pierson attachment. He condemns the position used in a Thomas splint. Altogether

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36. Lewis, K. M.: Russell Traction in Treatment of Fracture of Femur: Observation on One Hundred and Fifty-Six Cases, *Ann. Surg.* **113**:226-244 (Feb.) 1941.



the report seems somewhat biased and based on an extremely unfortunate experience with the use of skeletal traction.]

Swart<sup>37</sup> reports 6 cases of fractures of the femoral shaft in which he used two wire traction for control of the distal fragment. In 5 of the cases described there was anterior displacement of the distal fragment following the application of the Kirschner wire through the condyles with traction. This was overcome by the insertion of a second wire through the proximal end of the distal fragment and traction made in a downward direction. The same principle may be used when the distal fragment remains posterior with the traction then on the second wire in the upward direction. In the cases in which the fractures were treated by this two wire traction method the results were good. [Ed. NOTE: This simple method affords good control of the distal fragment in fractures of the shaft of the femur, and this control may be utilized with distinct advantage.]

Cubbins,<sup>38</sup> in a detailed article, covers the treatment of fractures of the shaft of the femur from the technic of the simple fundamental principles of skin traction, the use of which he advocates in the majority of cases, to a brief discussion of delayed union and nonunion. If skeletal traction must be used, a Steinmann pin is advocated rather than the Kirschner wire, and this is to be placed through the upper end of the tibia rather than through the lower part of the femur. The author contends that a Kirschner wire may cut from  $\frac{1}{2}$  to  $\frac{3}{4}$  inch (1.3 to 1.9 cm.) down through the condyles of the femur. This combined with the fact that there is a tendency of the wires to slide back and forth through the bone makes it more dangerous and uncomfortable than the larger pin. The operative attack is reserved for those fractures in which interposition of soft tissue is evident as well as for condylar fractures of the lower end. [Ed. NOTE: If the author accomplishes nothing else, he at least has stressed emphatically the conservative handling of these types of fractures. When skeletal traction is necessary, the Kirschner wire has been universally accepted because of the smaller caliber of the penetrating wound which results in less tissue destruction and makes the possibility of infection more remote. We seldom have had the complications with the Kirschner wire which the author outlines.]

*Fractures of the Patella.*—For fractures of the patella Dickson<sup>39</sup> describes an operative procedure utilizing a V-shaped strip of the

37. Swart, H. A.: Treatment of Fractures of Shaft of Femur by Double Wire Traction, *Am. J. Surg.* **52**:507-510 (June) 1941.

38. Cubbins, W. R.: Treatment of Fractures of Shaft of Femur, *Tr. West. S. A.* (1940) **50**:106-124, 1941.

39. Dickson, J. A.: Treatment of Fracture of the Patella, *Cleveland Clin. Quart.* **8**:154-157 (July) 1941.

quadriceps tendon which is left attached at its lower end and is of sufficient length to reach the tibial tubercle. After removal of the comminuted fragment of the fractured patella, this strip is fixed firmly to the previously reflected portion of the patellar tendon and the periosteum on the anterior surface of the patella. The transplanted portion of tendon aids in filling in the defect caused by removal of the fragments and reenforces the patellar tendon so that quadriceps exercises may be instituted in ten days and all protective dressing may be removed at the end of the third week. In the course of six weeks flexion to 90 degrees is to be anticipated. [ED. NOTE: This method is particularly indicated for the comminuted fractures, especially those in the lower pole of the patella, where excision of the small fragment and the retention of the major portion of the upper half are possible.]

Prince<sup>40</sup> reports a series of 14 cases of fractures of the patella in which partial excision of the bone was carried out with satisfactory results. The operative technic is similar to that uniformly used, namely, removal of the lower fragment or fragments and exposure of the upper fragment, which is securely sutured to the patellar tendon by mattress sutures of no. 2 or no. 3 chromic catgut. To obtain firm fixation of the patella three drill holes are made through its lower margin, extending downward and forward; through these the fixation sutures are threaded. Following careful repair of the fibrotendinous layer over the patella and the lateral portions of the capsule and the aponeurosis, the limb is immobilized in a light cast for two to three weeks. The patient is allowed to walk in ten days and permitted joint motions in the third week.

In a discussion of the various methods of treatment of this fracture the writer states that complete excision of the patella as advocated by some is too radical a procedure, although for the severely compound comminuted type this may be advisable. In 1 of his patients a good result with full extension and flexion to 90 degrees was obtained when the compounded upper fragment was removed and the quadriceps tendon was sutured to the distal fragment. He mentions also the value of this method in cases of malunion or nonunion of the patella, in which painful symptoms persist. [ED. NOTE: We heartily agree with the author in advising against complete removal of the patella when fractured.]

*Fractures of the Condyles of the Tibia.*—Buckner<sup>41</sup> states that fractures of the upper end of the tibia often result in poor function

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40. Prince, L. D.: Treatment of Fractures of the Patella by Partial Excision of Fragments, *Am. J. Surg.* **53**:232-236 (Aug.) 1941.

41. Buckner, H. T.: Fractures of Upper End of Tibia with Lateral Displacements, *Am. J. Surg.* **51**:707-721 (March) 1941.

because of damage to the ligaments of the knee and inadequate reduction. It is important for good function to restore the joint surface to as near to normal as possible. The author achieves this by drilling a hole across the upper end of the tibia and passing a wire through the fragments. The wire is threaded through a metal button on each side and is then twisted tight. The roentgenograms presented in this article reveal excellent replacement of the fragments. At the end of three weeks patients are allowed to begin weight bearing with a Thomas splint. [ED. NOTE: Bolts, nails and screws have been used for years in treating these fractures. The method of fixation with wire threaded through buttons may provide more secure reduction and fixation. At least it does in the hands of the author. The principal criticism of the method is the dependence on a twisted strand of wire for the whole support. Emphasis should be placed also on the importance of not allowing too early weight bearing in these cases.]

Wise<sup>42</sup> recommends combined traction and compression for bicondylar fractures of the tibia by the use of Kirschner wire traction through the os calcis and the compression by a sleeved wire<sup>43</sup> inserted through the tibial condyles. The point of insertion of the compression wire will vary, depending on the types of displacement and the level of the fracture. By gradual tightening of the nut on the other end of the wire the condyles are forced together.

If the sleeved wire is properly placed, compression of one or both condyles apparently is easily accomplished when adequate longitudinal traction through the os calcis is used. The compression sleeve used consists of three parts: (1) a Kirschner wire of medium diameter to which is welded a fixed metal bead and washer; (2) a metal sleeve which slips over the wire, and (3) a threaded collar with a setscrew and nut.

A case report illustrating the method shows anatomic reduction with a satisfactory functional end result.

The author suggests the use of this method of fixation for badly displaced fractures of this type, for which arthrotomy and open reduction are necessary.

Dobelle<sup>44</sup> reviews the various methods of treatment of fractures of the external condyle of the tibia, stresses the conservative method of handling this injury and describes a simple method which he has used in 5 cases with successful results.

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42. Wise, R. A.: Combined Traction-Compression Method for Treatment of Bicondylar Fractures of the Tibia, *Surg., Gynec. & Obst.* **72**:778-780 (April) 1941.

43. The sleeved wire can be obtained from the De Puy Manufacturing Company, Warsaw, Ind.

44. Dobelle, M.: New Method of Closed Reduction of Fracture of Lateral Condyle of Tibia, *Am. J. Surg.* **53**:460-462 (Sept.) 1941.

The technic consists first of all of the application of a foot, leg and thigh cast with the leg in complete extension. Particular attention is paid to padding the outer upper aspect of the thigh and the medial aspect of the knee. In the cast are incorporated a pair of ordinary hinges, one anteriorly and the other posteriorly, eccentrically placed at an angle of about 30 degrees with a convexity mesialward and with apexes centered over the knee joint proper. Elliptic sections of the plaster are removed on each side of the hinges, and the leg is gradually brought into as much varus as desired. A wooden block is then inserted as a strut against the lateral cuts of the cast edges at the posterolateral aspect. In addition, molding of the comminuted mass is done by blows with a rubber mallet, and then lateral compression is applied with a furniture clamp.

In the 5 cases absolute immobilization was carried out for ten weeks and was followed by the application of a walking caliper brace. No weight bearing was allowed for six months. The final end results were gratifying; painless freely movable joints were obtained.

*Dislocations of the Knee.*—Wilson, Michele and Jacobson<sup>45</sup> report 6 cases of complete dislocation of the knee joint without complicating fractures involving the joint occurring over a period of thirteen years. Excellent results were obtained by conservative treatment consisting of immediate manipulative reduction and plaster fixation. One patient had an exploratory operation, but no ligamentous repair was attempted. All patients were male, ranging between 15 and 35 years of age, except one, who was 63 years. Each patient had a good result with apparent spontaneous repair of the internal ligaments of the knee.

In the opinion of the writers there is no indication for repair of cruciate ligament injuries until conservative methods have failed, and they suggest at least one year of observation before attempting any of the various methods of reconstruction for cruciate ligament laceration.

[ED. NOTE: This study of 6 cases of a rare injury should be carefully reviewed by all radically minded surgeons who advocate immediate operative repair. In spite of variable degrees of instability, the functional end result in cases of this type is often surprisingly good.]

*Fractures of the Tibia and the Fibula.*—DeGoes<sup>46</sup> presents a clinical study of 50 cases of fracture of the shaft of the tibia. The author rightly emphasizes the ease of early reduction compared with late reduction. He favors traction on the Braun frame followed by the use of a plaster

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45. Wilson, M. J.; Michele, A. A., and Jacobson, E. W.: Complete Dislocation of Knee Joint: Report of Six Cases with End Results, *Am. J. Surg.* 52:77-81 (April) 1941.

46. deGoes, H.: Technic of Treating Diaphysial Fractures of the Tibia. *Rev. brasil. de cir.* 10:15-34 (Jan.) 1941.

cast and the insertion of pins above and below the fracture when necessary. His 2 delayed unions occurred when the fibula was intact, and he advises osteotomy of the fibula to permit proper traction on the tibia. [ED. NOTE: This is an excellent way to overcome the tendency to interference of union caused by the intact fibula. Wedging the cast to overcome angulation is likewise stressed, and this also is a simple means of perfecting the position of the fragments.]

Juers<sup>47</sup> discusses briefly the treatment of fractures of the tibia and the fibula, emphasizing the necessity of putting the cast from the groin to the toes with the knee slightly flexed. He recommends the use of a stirrup, including a windlass, to obtain traction with a Steinmann pin through the heel for comminuted or oblique fractures. This permits a certain amount of ambulatory treatment in cases in which traction is necessary. The windlass consists of a rotating bar, a key inserted in a metal stirrup; this in turn is incorporated in the cast in the lateral position.

Mansfield<sup>48</sup> reviews 15 cases of oblique fracture of both bones of the leg seen in 1939 at the United States Marine Hospital, Detroit. It was found that in 60 per cent of the cases sharp fragments were caught in muscle or other soft tissue and that this prevented accurate closed reduction. If the fractures were explored early and the fragments were wired in normal position, the bones healed more promptly, and the cost of treatment was less. [ED. NOTE: It is true that oblique fractures of the tibia are difficult to reduce even when the fibula also is fractured. On the other hand, when both bones are fractured, there are few cases of delayed union or nonunion of fractures of the tibia with closed methods of treatment.]

Jensen<sup>49</sup> had an opportunity of observing 12 fractures of the fibula from overstrain at an aviation hospital. The patients were between 18 and 20 years of age. All had been hurt while vaulting. The injury in all cases was located about a handbreadth below the head of the fibula. The patients came for treatment for pains in the leg which they themselves attributed to the muscles. In many cases the fracture was difficult to demonstrate in roentgenograms and could frequently be visualized in these only through a lens. Jensen asserts that fractures from overstrain occur frequently in hitherto normal bones, so that previous fractures can hardly be considered as the responsible factor. In 9 of the cases

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47. Juers, E. H.: Fractures of Distal Half of Tibia and Fibula, *Minnesota Med.* **24**:172-174 (March) 1941.

48. Mansfield, R. D.: Treatment of Oblique, Spiral Fractures of Both Bones of Leg: Analysis of Fifteen Cases Treated by Open and Closed Methods, *J. Bone & Joint Surg.* **23**:910-916 (Oct.) 1941.

49. Jensen, W.: Fractures of Fibula Due to Overstrain, Twelve Personal Cases, *Zentralbl. f. Chir.* **67**:2148-2153 (Nov. 16) 1940.

presented there was more or less pronounced weakness of the connective tissue as evidenced by epigastric hernia and foot deformities. Eight of the patients had pronounced acrocyanosis; this indicates a definitely deficient circulation. Eight patients complained likewise of muscular cramps in the leg or of muscular induration. In 4 cases cramps had been present some days before the injury, and in the other muscular indurations were reported as occurring at the time of injury. The author states that there is an analogy between these fractures and those occurring in association with metrazol and insulin shock. He expresses the opinion that these muscular lesions may be considered as evidence of disturbed glycogen metabolism directly related to the vascular system which is not equal to the sudden strain and that during the course of development of muscular cramps and indurations a vicious circle is instituted. The author suggests the name "myogenic fracture" for such lesions.

*Fractures and Dislocations of the Ankle.*—Brothers<sup>50</sup> reports that with the greater enthusiasm for winter sports, a new injury (ski fracture) of the ankle has appeared. Overzealous amateurs and unskilled exhibitionists account for most of them. In this injury the point of the ski turns out, and the patient falls forward, thus producing sharp outward rotation and extension of the ankle. There is nearly always a spiral fracture of the lower end of the fibula, but the internal malleolus is not broken. The potential seriousness of the injury comes from tearing of the ligaments of the ankle joint proper. Such accidents are prevented by adequate instruction beforehand, avoidance of fatigue (most cases occur in the late afternoon) and proper consideration of the hazards of bad weather. [ED. NOTE: From the military angle this presentation is of much potential importance today.]

Selig<sup>51</sup> describes briefly 2 cases of disability due to unreduced dislocation of the posterior marginal fragment in fractures of the ankle. A large number of painful disabling ankles are due to this condition. Lateral displacement is usually recognized and effectively reduced and maintained, but posterior displacement is sometimes overlooked. There is little in the literature on this subject. Scudder and others have mentioned the difficulties it may produce. Cotton states that unless such dislocation is reduced it may result in serious disability in many instances. Selig discusses the technic of treatment recommended by Watson-Jones and Böhler. Not all such dislocations are difficult to reduce. They are most easily reduced if the fracture is recognized and

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50. Brothers, W. W.: Ski Injuries at Sun Valley. Discussion of Causes, Unusual Type of Fracture and Treatment, *Northwest Med.* **40**:14-16 (Jan.) 1941.

51. Selig, S.: Posterior Marginal Fragment in Fracture of Ankle, *J. Mt. Sinai Hosp.* **7**:497-502 (Jan.-Feb.) 1941.

treated by proper manipulation. The correction of lateral displacement of Pott's fracture will not correct the posterior displacement.

The technic for reduction of the posterior displacement is described as follows: With the patient under anesthesia traction is exerted on the tarsus in a distal direction. When traction is maintained, the surgeon gradually changes the direction of force to a straight upward pull to the ceiling with simultaneous reduction of equinus until the foot is at right angles with the leg. If this attempt fails it should be repeated with the knee flexed to 90 degrees to relax the gastrocnemius muscle. Associated malleolar fractures must also be reduced. In applying the plaster extreme inversion of the foot must be avoided. If possible, the foot should be immobilized in a neutral position at an angle of 90 degrees to the leg. The plaster cast is applied from the toes to the mid thigh with the knee at 90 degrees flexion. If the ankle is badly swollen, immobilization can be accomplished by a wire through the os calcis until the edema subsides.

The original plaster should be changed in four or five weeks to a walking cast extending to the tibial tubercle. The time for change varies with the severity of the case. After removal of the cast, a gelatin bandage or firm adhesive is applied from the toes to the tibial tubercle. Little physical therapy is needed to restore normal function to the ankle joint. If reduction has been unsatisfactory, prolonged physical therapy is required, and even with this there may still develop traumatic arthritis between the astragalus and the tibia so that fusion may become necessary.

*Fractures and Dislocations of the Astragalus.*—Miller and Kolb<sup>52</sup> report 2 cases of talonavicular dislocations and include a brief review of some 139 reported cases, indicating the various types and that the inward dislocation is the most common. In 1 of their cases reduction was easily obtained by manipulation; in the other case operation was required. They conclude that if the dislocation cannot be reduced with the patient under anesthesia after comparatively mild manipulation, it is better to wait ten days for the edema to subside and then do open reduction. In both of the cases excellent functional results were obtained. [ED. NOTE: In cases in which the patient is seen early, it is difficult to understand deliberately postponing operative reduction, unless there is some contraindication for operation, e. g. in the nature of the condition of the patient or the condition of the skin.]

McCurrich<sup>53</sup> reports the unusual case of complete expulsion of the astragalus in a young sailor whose ship struck an unsuspected mine.

52. Miller, L. F., and Kolb, L. H.: Talonavicular Dislocation, *Am. J. Surg.* **51**:439-441 (Feb.) 1941.

53. McCurrich, H. J.: Traumatic Expulsion of Astragalus, *Brit. J. Surg.* **28**: 611-614 (April) 1941.

The exact mechanism of injury is not known, but the patient was blown into the air, falling into the water, sustaining injury of the soft tissue in the left shoulder, which was more painful than the marked compound dislocation at the ankle.

Roentgen examination disclosed complete absence of the astragalus, with a transverse fracture of the external malleolus. The compound injury was over the medial aspect of the ankle with all tendons as well as the posterior tibial vessels and nerves lacerated. Because of the severe injury to the soft tissue, amputation was necessary.

A discussion of the mechanism of the injury indicates that the foot was violently displaced laterally with consequent fracture of the fibula and laceration of all the structures on the medial side of the foot from stretching. This permitted the expulsion of the entire astragalus from the foot.

In reviewing the literature the writer finds only 1 case in which the astragalus was completely dislocated and lying between the skin and the patient's sock. In this case the bone was replaced and a satisfactory result obtained.

[ED. NOTE: There is no doubt but that complete compound dislocation of the astragalus is more frequent than the surgical literature indicates. Such an injury is a major one, and the treatment and the functional results in a case of such an accident should always be reported.]

Milch<sup>54</sup> reviews the historical background of fractures of the processus posticus tali, pointing out that in the French literature this lesion goes by the name of Cloquet's fracture. In the English literature, however, credit is given to Shepherd, who reported this rare lesion at the Medical and Surgical Society of Montreal in 1882. The recent work of Carnevali has supplied the microscopic evidence to confirm the opinion that this rare fracture actually does take place.

Shepherd attempted an experimental reproduction of this fracture and called attention to the facts (1) that the processus posticus tali is situated lateral to the groove of the flexor longus hallucis tendon, (2) that the size of the processus varies and (3) that the position of the fasciculus of the lateral ligament of the ankle joint was attached to the tip of the processus posticus of the astragalus. When the foot becomes plantar flexed, the posterior part of the astragalus rises upward and approaches the lower margin of the posterior surface of the tibia. Impingement of the tibial margin against the tip of the processus leads to a torque with consequent fracture at the side of the fulcrum.

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54. Milch, H.: Fracture of Processus Posticus Tali, M. Rec. **154**:90-92 (Aug. 6) 1941.



The condition must be diagnosed on the basis of the mechanism of injury, localized tenderness, pain with plantar flexion of the foot and also acute flexion of the great toe. Roentgen evidence should show a sharp irregular fracture surface as against the smooth outline of a typical os trigonum.

The author reports a case in which there is an unquestioned fracture of the processus. After ten days' immobilization in plaster, a check-up roentgen examination with the foot in equinus position and then in calcaneus position showed an upward shifting of the fragment in relation to the body of the astragalus when the foot was in the first position.

The prognosis is good after a short period of fixation in plaster. There is no indication for resection of the fragment unless it acts as a bony block.

DeAraujo<sup>55</sup> reports a case of isolated fracture of the external apophysis of the astragalus in detail, the second he has observed. The lesion is a rare one, there being only 5 cases reported in the literature. He emphasizes that diagnosis is difficult, most of the published cases having been confused with a tibiotarsal accessory bone, as was the first case reported by the writer. Careful examination of the anterior portion of the external malleolus will yield an excellent point from which to examine the astragalus and in particular the external apophysis. Palpation will reveal crepitation and a site of maximum pain. The author states that the lesion is caused by abnormal torsion movements of the astragalocalcaneal and calcaneoscaphoid articulations. In his second case there had been a sudden violent external rotation of the knee with the foot fixed on the ground, causing torsion of the subastragalar joint with fracture of the external apophysis of the astragalus. All 5 cases occurred in male patients in the second or third decades of life, and all fractures were on the left side. In all cases cure was effected in four to six weeks by simple immobilization. The accidents occurred during work. [ED. NOTE: This fracture is seen in industry probably more often than in civilian life. It occurs more often than reports in the literature indicate.]

*Fractures of the Os Calcis.*—Ahlberg<sup>56</sup> reports the results of final examinations in 111 cases in which there were one hundred and twenty-two fractures of the os calcis during the period 1925 to 1937. In the present article he deals with ninety-five fractures in 88 patients. The fractures are of a more severe variety with direct or indirect involvement of the joint roughly corresponding to Böhler's groups V to VIII. In at least 60 per cent the accident had taken place five years earlier.

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55. deAraujo, A.: Isolated Fracture of External Apophysis of the Astragalus, *Rev. brasil. de orthop. e traumatol.* 2:277-285 (March-April) 1940.

56. Ahlberg, A.: Therapeutic Results in Severe Fractures of the Calcaneum. *Acta chir. Scandinav.* 84:187-198, 1940.

Complete anatomic restoration was not observed in any case, not even when early active therapeutic measures had been undertaken. Mobility in the subastragaloid joint was found to be normal in only 6 cases. In the rest it was either absent or limited. Mobility seems independent of whether the joint surfaces are anatomically restored or not. For years numerous patients had had painful symptoms after the accident, as a rule apparently caused by injuries of the joint. Changes in the joint occasioned by fracture seem to develop irrespective of the therapeutic methods and are according to the nature of the fracture. The author agrees with those writers who after the earliest possible reduction advocate performing subastragaloid arthrodesis four to five months after the accident if symptoms persist.

Campbell<sup>57</sup> reports 1 case of transverse fracture across the body of the calcaneus with upward-backward rotation of the posterior fragment. The fracture was reduced by insertion of a Steinmann pin horizontally in the back of the posterior fragment. With this pin as a lever, the tension against the heel cord was counteracted by a downward pull on the pin, and the whole was incorporated in the cast. Campbell includes no follow-up in the 1 case reported. [ED. NOTE: This seems to be a rather ingenious method of reduction applied to this particular situation.]

*Fractures and Dislocations of the Spine.*—Barber<sup>58</sup> reported a case of a fracture of the spine with dislocation of the first lumbar vertebra on the second lumbar vertebra and loss of motor and sensory function in the right leg. Attempted manipulation with the patient under anesthesia did not reduce the dislocation. When the vertebrae were exposed at operation, the dislocation was easily reduced, and the spinous processes were anchored with a wire loop to prevent redislocation. Pressure symptoms on the cord gradually disappeared, and the patient eventually made a satisfactory recovery. [ED. NOTE: This ingenious operation which overcame the disability is well worth while in the treatment of irreducible dislocations of the spine. The author makes the excellent point that the surrounding soft tissues are sometimes so lacerated that the vertebrae must be fastened together to prevent recurrence.]

Outland<sup>59</sup> emphasizes the importance of accurate diagnosis and early adequate treatment for fractures of the spine, indicating that too

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57. Campbell, W. G.: Simple Operation for Reduction of Fragments of Os Calcis, *Brit. M. J.* 2:651-652 (Nov. 8) 1941.

58. Barber, C. G.: Open Surgical Reduction of Fracture-Dislocation of Lumbar Spine with Cord or Cauda Equina Involvement, *Am. J. Surg.* 52:238-245 (May) 1941.

59. Outland, T.: Treatment of Compression Fractures of Spine, *Pennsylvania M. J.* 44:866-868 (April) 1941.

many of these patients are treated by surgeons who are insufficiently trained in fracture operations. He indicates that residual disability is due to one of three things: (1) actual deformity causing angulation of the spine; (2) disturbance of the lateral intervertebral joints due to subluxation; (3) neurotic fixation. He prefers to use a local anesthetic, injecting 30 to 40 cc. of 0.5 per cent procaine hydrochloride directly into the hematoma. He says this is not a difficult procedure and can be readily done. The reduction is carried out with the patient in a prone position, and a body cast is applied with great care. The author stresses the importance of after-care and feels that it is particularly important that the patient be allowed to be up immediately and even to undertake light work. In the absence of this active regimen definite exercises are given and carefully supervised in order that there be good function when the cast is removed from three to six months later. He feels that ordinarily a brace is not necessary and in fact may often do harm, psychologically at least. [ED. NOTE: This review is included because several of us fully disagree with the author with regard to early weight bearing. Few patients with compressed fractures of the spine should be allowed early weight bearing. Also a cast or brace should be worn until sufficient union has taken place. Serious complications can result from failure to observe these measures.]

Greenwood<sup>60</sup> describes a simple method of fixation of the spinal column in hyperextension for compression fractures of the thoracic and lumbar vertebrae. A double Balkan beam, a table and plaster of paris are necessary. The patient is placed in the supine position. Anterior and posterior plaster slabs are placed on the trunk, the anterior extending from the suprasternal notch to the symphysis pubis. While these are setting, a heavy cloth bandage is carried as a sling around the posterior slab at the fracture site and brought up over the horizontal bars of the double Balkan beam, and the body is raised until the buttocks and the shoulders swing clear of the table. When the two heavy plaster slabs have become firm enough to retain their shape, they are incorporated in a circular plaster body cast.

The author stresses the simplicity of the method and the fact that the patient is in the more comfortable supine position. It is especially suitable for patients with mental diseases who have sustained thoracic fractures during convulsive shock treatment for schizophrenia and other conditions.

Gullikson and Anderson<sup>61</sup> review various methods of treatment of fractures of the spine and report end results in 34 cases. Their suggested method is the use of a suspension sling (as for fractures of the

60. Greenwood, H. H.: Fixation of Fractured Vertebrae, *Lancet* 1:754 (June 14) 1941.

61. Gullikson, J. W., and Anderson, E. R.: Compression Fractures of Dorsolumbar Vertebrae, *West. J. Surg.* 49:576-580 (Oct.) 1941.

pelvis) with production of gradual hyperextension. The application of 40 to 50 pounds (18.1 to 22.7 Kg.) to an overhead traction pulley arrangement is advocated. The authors contend that this is more comfortable than the Bradford frame and safer than rapid reduction with the patient under anesthesia. After four to ten days a body jacket is applied with the patient on a Roger's hammock frame. Ambulation is permitted in two to three days. At the end of two to three months a Taylor brace is fitted; this is worn for about two months. Return to work is usually possible six to eight months after injury.

Analysis of the cases of 34 patients with an average age of 45.2 years showed an average disability period of eight and two-tenths months. Thirty-two of the patients returned to their former work, and 16 were symptom free. Fifteen had occasional backaches, and 2 were unable to return to their regular duties. Associated skull fractures were found in 7; 14 had more than one vertebra fractured, and 2 had early symptoms of compression of the cord. One patient was operated on because of the damage to the cord and recovered. There were no deaths. The Soto-Hall sign (acute flexion of the neck producing pain at the fracture site) is stressed as a diagnostic aid.

Haggart<sup>62</sup> reports in detail a fracture-dislocation of the lumbar spine with forward displacement of the third lumbar vertebra on the fourth, and fragmentation of the laminae and articulations between the third and fourth lumbar vertebrae associated with incomplete paralysis of the lower extremities and loss of bladder and anal sphincter control. The patient was seen three weeks after injury, and after tidal drainage of the bladder was instituted, open operation was performed with reduction of the fracture-dislocation. Reduction was maintained by wire lashed in a crossed fashion through the spinous processes of the third and fourth lumbar vertebrae in addition to fusion of the spine with bone chips obtained from the right posterior part of the ilium.

The end result one year after operation disclosed the patient as ambulatory without support. There was complete control of the sphincters and only slight weakness of the right leg. Roentgen examination showed firm bony fusion of the lumbar portion of the spine with maintenance of the reduction.

[ED. NOTE: This case represents one of the positive indications for operative procedure in the treatment of spinal injuries. Manipulation, no doubt, would have caused increased damage to the cauda equina and failure of reduction of the dislocation. The fusion of the spine following the reduction may not have been absolutely necessary, but in this patient with extensive osteoarthritis the end result no doubt was better because of fixation of the lumbar portion of the spine.]

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62. Haggart, G. E.: Fracture-Dislocation of the Lumbar Spine, Open Reduction and Fixation by Spine Fusion: Case Report, *Lahey Clin. Bull.* 2:177-185 (Oct.) 1941.

Wortis and Sharp,<sup>63</sup> in a comprehensive review, study 200 cases of fractures of the spine at various levels. Of particular interest is the curve of incidence of specific areas of injuries which shows the commonest sites to be at the levels of the second cervical and the sixth cervical vertebra and in the dorsolumbar region. Of 52 patients with fractures of the cervical portion of the spine 75 per cent showed evidence of injury to the spinal cord or root. Seventy-five per cent of the patients who had neurologic signs died. Fifty per cent of the patients with cervical injuries showed evidence of cerebral concussion. In the 40 cases in which there was a fracture of the thoracic portion of the spine 58 per cent of the patients showed evidence of the injury to the spinal cord or root, and in this group 52 per cent of those with neurologic signs died. Of the 104 patients with fractures of the lumbar portion of the spine only 24 per cent showed evidence of injury to the spinal cord, and only 1 patient died. All 4 patients with fracture of the sacral part of the spine recovered; none presented neurologic signs.

Of the 15 patients on whom laminectomy was performed only 2 showed improvement. This led the writers to adopt a conservative attitude. Surgical intervention, which should always be done extradurally, is indicated: (1) when the lamina of the spine is fractured, causing cord compression, in which case hyperextension is apt to increase pressure on the cord; (2) when there is an incomplete cord lesion and definite evidence of bone fragments in the spinal canal; (3) when the patient with signs of an incomplete lesion of the cord shows evidence of progressive cord dysfunction despite reduction and immobilization (this group is the only one in which manometric studies of the spinal fluid are of value); (4) when bony compression injures the fibers of the cauda equina, and (5) when there is intractable pain in the root secondary to fracture of the body or of a lamina. One important fact which is emphasized is that with hemorrhage in the spinal cord this hemorrhage is most apt to extend into the gray matter. When flaccid paralysis rather than spastic paraplegia is present, the prognosis is grave. A patient in this condition should never be operated on.

Some of the indications for late operative intervention are as follows: (1) callus encroachment in the spinal canal giving slowly increasing neurologic signs; (2) callus encroachment on the spinal root with intractable pain; (3) herniation of an intervertebral disk; (4) hypertrophy of the ligamentum flavum with increased pressure of the spinal cord; (5) post-traumatic adhesive arachnoiditis.

The writers urge optimism in spite of what at first appears to be a severe injury to the spinal cord. Conservative care is stressed unless

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63. Wortis, S. B., and Sharp, L. I.: *Spine Fractures: Study of Two Hundred Cases*, J. A. M. A. **117**:1585-1591 (Nov. 8) 1941.

there is positive indication for laminectomy. There is less reason for optimism in cases of flaccid paraplegia and in the presence of the Gordon Holmes slow flexion reflex. The presence of a Babinski sign in the first three weeks after severe injury is a good omen. [ED. NOTE: This is a splendid review of spinal injuries from the neurologic standpoint and is especially valuable for its presentation of prognostic signs, the wisdom of its conservatism and its limitation of indications for laminectomy.]

Hatchette<sup>64</sup> points out that isolated fractures of the atlas are extremely rare, there being only 99 cases reported since 1822. He discusses the reasons for infrequent injury to this bone: first, that there is no body to be damaged by wedge action of forward flexion; second, that the major force of the blow vertically is divided between the two wedge-shaped lateral masses which give good support. He indicates that the causation of fracture is forcible vertical pressure, separating the two lateral masses, and so fracturing the ring of the atlas. One case is reported.

Weissberg and Reinstein<sup>65</sup> outline the accepted theories of spontaneous subluxation of the atlantoaxial articulation or Grisel's syndrome. This was first reported by Wittek in 1908 and is a rare cause of wry-neck. The theories are: (1) effusion into the joint with overdistention of the ligaments; (2) incoordinate reflex action; (3) contracture of the suboccipital muscles secondary to nasopharyngeal lymphadenitis, and (4) rupture of the transverse ligament at the atlas.

The actual dislocation is preceded in most instances by infection of the upper part of the respiratory tract. It is seen most frequently in children, although the authors' patient was a white man aged 52 years. One week before admission to the hospital this patient had infection of the upper part of the respiratory tract. This was followed in two days by acute pain, muscle spasm and complete fixation of the cervical portion of the spine. Roentgen examination disclosed forward displacement of the body of the atlas on the axis. Reduction was easily accomplished, as is usually the case, by continuous head traction followed by plaster fixation. [ED. NOTE: Approximately 30 cases have been reported up to the present time, and one of us (H. E. C.) had a similar lesion in a youngster in whom spontaneous anterior dislocation developed after a prolonged illness when the sitting position was assumed. In another case a 19 year old girl had infection following tonsillectomy. In the latter patient paralysis of the upper extremities developed. This cleared up with rest in bed and traction. Later a rigid support was applied to the neck and the back.]

64. Hatchette, S.: Isolated Fracture of Atlas, *Radiology* 36:233-235 (Feb.) 1941.

65. Weissberg, J., and Reinstein, H.: Spontaneous Dislocation of Atlanto-Axial Articulation: Report of Case, *New York M. Coll. & Flower Hosp. Bull.* 3:306-308, 1940.

Six cases of dislocation of the cervical vertebrae are reported by Willard and Nicholson<sup>66</sup>—3 each of the traumatic and spontaneous types. No neurologic symptoms were noted, and reduction was possible in all cases except 1 in which it could not be maintained because of an uncooperative patient with subsequent death from pneumonia. All the traumatic dislocations were associated with fractures of the odontoid process. The 3 spontaneous dislocations followed infections of the upper part of the respiratory tract and cervical adenitis. One dislocation was posterior with associated fracture of the odontoid.

The treatment except in the patient with the posterior dislocation was by the dependent head method previously described by Nicholson which permits gentle spontaneous reduction in twenty-four to forty-eight hours with the head gradually extended over the edge of two or three mattresses placed on a fracture bed with the patient held in position by Buck's extension. Following reduction plaster fixation from the head to the pelvis for twelve to sixteen weeks and the use of a Thomas collar for six to eight weeks are recommended. In 1 case with three recurrences in fifteen months, the method of Mixter and Osgood was utilized, the arches being lashed together with a strip of fascia lata.

This presentation in addition to giving detailed case studies reviews the classification, the causation, the anatomic features, the diagnosis and the treatment in a thorough manner. The outstanding features were the infrequency of neurologic complications, the safety and the ease of spontaneous reduction with the head hanging dependent (except in cases of posterior dislocations) and the operative fixation with fascia lata in cases of recurrent dislocations.

Wright and Wunderly<sup>67</sup> describe a mobile traction apparatus for use in treating fractures or dislocations of the cervical vertebrae. The device has for its basis traction through a palatal piece which fits over the teeth of the upper jaw; this gives fixed traction to the cranial skeleton, which withstands considerable pressure without injury, and a broad flat base on the occiput for countertraction. A plate bearing evenly on the teeth of the upper jaw is made of aluminum and is attached to two stainless steel arms, curving about the cheeks and attached to a molded aluminum trough lined with thick sponge rubber in which the occiput rests. The molded frame is mounted on a roller skate to give mobility to the apparatus. To this frame a bow of meccano iron is fixed to pass around the forehead; to the bow are attached the cheek bars of the palatal part. It is also suggested that

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66. Willard, DeF. P., and Nicholson, J. T.: Dislocation of First Cervical Vertebra, *Ann. Surg.* **113**:464-475 (March) 1941.

67. Wright, R. D., and Wunderly, J.: Treatment of Fracture or Dislocation of the Cervical Vertebrae, *M. J. Australia* **2**:532-534 (Nov. 23) 1940.

instead of the trough for the occiput being made out of aluminum one be made out of a plaster mold. In edentulous upper jaws the palate should be completely covered with an aluminum plate rather than just the palatal bar. The advantages are ease of modification of flexion and extension of the neck as well as alteration of the pull from side to side. The mouth can be opened easily for eating and speaking, and the palatal part can be removed for hygienic care of the upper teeth.

A report of a case is given in which the patient was a 14 year old girl with a fracture-dislocation of the fourth and fifth cervical vertebrae and a compression fracture of the seventh cervical vertebra seen seven weeks after injury. With the palato-occipital traction apparatus, gradual increasing weight up to 16 pounds (7.3 Kg.) was possible with little discomfort. Satisfactory reduction was obtained.

[ED. NOTE: This complicated apparatus makes it necessary to obtain an impression of the upper dental arch and to construct from this a palatal bar of aluminum or vulcanite.]

*Metrazol Fractures of the Spine.*—Read<sup>68</sup> reports on the consequences of metrazol therapy in a long series of 320 patients with schizophrenia. He points out that in 20 to 30 per cent of cases in which metrazol therapy is used vertebral fractures develop. However, after this percentage was realized, the last 50 patients treated apparently had no fracture whatever. They were supported by being firmly held to a sandbed, indicating that with proper support the percentage of fractures should drop materially. [ED. NOTE: This is a careful report and seems to indicate that with the recognition of the danger the percentage of vertebral fractures markedly diminished in many of these conditions of the convulsive type.]

To determine the frequency and the seriousness of complicated vertebral fractures in patients with epilepsy of the grand mal type, Moore, Winkelman and Solis-Cohen<sup>69</sup> selected 12 such patients at random. Ninety-two per cent showed some form of vertebral injury; 66.67 per cent showed definite compression fractures of the thoracic and lumbar vertebrae. In all but 1 case there were no symptoms referable to the vertebral column. There were no orthopedic or neurologic disturbances as a result of these vertebral defects.

The purpose of their study is to defend the use of metrazol in the treatment of types of neuropsychiatric conditions in which it has shown itself to be of considerable value. In spite of the frequency of spinal injuries with this therapy, it is thought justified to continue its use,

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68. Read, C. F.: Consequences of Metrazol Shock Therapy. *Am. J. Psychiat.* **57**:667-676 (Nov.) 1940.

69. Moore, M. T.; Winkelman, N. W., and Solis-Cohen, L.: Asymptomatic Vertebral Fractures in Epilepsy, Comparison with Vertebral Fractures Due to Metrazol Induced Convulsions, *J. Nerv. & Ment. Dis.* **94**:309-323 (Sept.) 1941.



and a suggestion is made how to avoid compression fractures as much as possible. This consists of using a hard even mattress with fracture board between it and the springs so that there will be no chance for acute flexion during the convulsive seizure. In addition, attendants hold the patient squarely on his back and also control the lower jaw to prevent fracture of the mandible and biting of the tongue.

[ED. NOTE: While in most instances acute flexion may account for the compression fractures, often during the convulsive seizure the patient remains straight, and the injuries which occur are due to violent muscle spasm rather than to assumption of the jackknife position.]

*Fractures of the Jaw.*—Coleman<sup>70</sup> states that in 1913 he described a sign for fracture of the mandible ignored in textbooks except in the recent treatise by James and Fickling.<sup>71</sup> The sign is produced by an effusion of blood into the tissues of the floor of the mouth and gives rise to a characteristic appearance of its mucous membrane, which becomes raised and forms a bluish, tense and elongated swelling under the side of the tongue. The sublingual fold lying between the tongue and the mandible is the part chiefly involved in this effusion. This sign alone will serve to differentiate an external bruise from an injury producing a fracture of the jaw.

In 1909 the author devised a clamp for fixing the fragments of a broken jaw. The clamp consisted of a strong steel spring which could be opened to enclose the fractured ends of the bone and which when released embedded itself in the mucous membrane and bone by means of its projecting claws. The method of applying the clamp is described. The clamp has been slightly modified since making it a little more powerful and facilitating removal. It must be removed by the operator.

McGrail and Doherty<sup>72</sup> discuss the difficulty of accurate roentgen visualization of fractures through the neck of the mandible, which is the most common type of fracture of the jaw. They suggest the following technics: (1) the technic used for visualization of the mastoid region with the tube at an angle of 45 degrees; (2) a technic in which the cassette is parallel to and against the side of the face, the central ray passing through the sigmoid notch and the chin being turned toward the tube; (3) visualization of the zygomatic arch with an intraoral technic. In the last-named method the dental film is held in the teeth, projecting out into the cheek as far as possible, the tube being aimed from above and the head being deviated slightly away from the injured

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70. Coleman, F.: Fractured Mandible: Sign of and Method of Treatment. *Proc. Roy. Soc. Med.* **34**:212-214 (Feb.) 1941.

71. James, W. W., and Fickling, B. W.: *Injuries of the Jaws and Face*. London, John Bale & Staples, Ltd., 1940.

72. McGrail, F. R., and Doherty, J. A.: Roentgenograms of Mandibular Condyle and Zygomatic Arch, *Am. J. Roentgenol.* **45**:637-639 (April) 1941.

side. Views taken by these three technics give accurate roentgen visualization of the fractured area and permit accurate analysis of the type of injury.

Strock<sup>73</sup> emphasizes the importance of simplifying the forms of treatment which may be applied to simple or complicated fractures of the mandible. He illustrates the displacement of the fragments at various levels and how they are influenced by muscular pull. The direction of the line of fracture also governs the displacement.

Two principles, namely, prompt reduction and simplicity of immobilization, are stressed. The latter is accomplished by intermaxillary wiring. Buttons are made by carefully twisting the properly placed loops of wire, and onto these are looped short elastic bands as used in orthodontia. Bands may also be cut from rubber tubing. With this arrangement the jaws are held in occlusion without force, and the slight movement possible stimulates healing.

The most important guide to proper alinement is occlusion. It is important to know whether abnormal occlusion was present before the fracture. The rule without exception is that no tooth without an occluding tooth in the opposite jaw should be used to support a button to which elastic traction is applied. Intermaxillary elastics are easily replaced to permit more thorough cleansing of the oral cavity and give a constant, thorough and gentle force in fractures delayed in reduction. The author considers shorter immobilization desirable, having removed the wires within fifteen days in some cases.

Griffin<sup>74</sup> describes an ingenious technic in which a special skeletal fixation splint is used for reduction and fixation of fractures of the mandible which permits free movement of the lower jaw, thus making it possible for the patient to masticate semisolid foods as well as permitting more adequate oral hygienic care.

The apparatus consists of either stainless steel or vitallium fixation screws applied externally through small incisions into each fragment; to these are attached a cross block with the usual screw adjustments in order to bring the fragments into apposition. The entire apparatus weighs approximately  $1\frac{1}{2}$  ounces (46.7 Gm.), which is not sufficient to interfere with movements of the mandible. Following removal of the screws after union is adequate to permit discontinuance of the use of the apparatus, the four stab incisions are freshened and sutured with fine dermal sutures. According to the author the indications for the use of this technic are unlimited, but it is particularly valuable in fractures of the molar or premolar region with long edentulous posterior frag-

73. Strock, M. S.: Fractures of the Mandible, Surg., Gynec. & Obst. **72**:1047-1051 (June) 1941.

74. Griffin, J. R.: Treating Fractures of Mandible by Skeletal Fixation. Am. J. Orthodontics (Oral Surg. Sect.) **27**:364-376 (July) 1941.

ments or in completely edentulous jaws, where wiring is impossible. The method is particularly indicated in compound fractures, such as gunshot wounds, in which large fragments of bone may have been lost. It is considered an ideal type of splinting following a bone graft for nonunion. Three cases are reported and generously illustrated; the results were apparently satisfactory.

Mowlem and associates<sup>75</sup> describe an apparatus for fixation of fractures of the mandible extraorally in patients who have no teeth and in whom the fracture occurs behind the tooth-bearing area. A pair of crossed Kirschner wires are inserted into each fragment; these in turn are locked on plates which are attached together by an intervening fixation bar. The advantage of the apparatus is the relative comfort obtained without locking the mandible to the upper jaw, thus permitting oral cleanliness and eating with ease. The locking plate and the fixation bar are made of aluminum alloy and together weigh less than  $\frac{1}{2}$  ounce (15.5 Gm.). The minute scars made by the Kirschner wires are easily excised and negligible. This apparatus has been used by the writers in 19 cases. They suggest that its use be limited to those fractures which cannot be adequately controlled by standard methods.

Ivy<sup>76</sup> writes that preparations have been made in the office of the Surgeon General of the United States Army for a more systematic plan of treatment of gunshot wounds of the jaws than that used in the first World War. Special training is being given to medical and dental officers and enlisted men in the medical department, who will be assigned to units from the combat zone back to the general hospital. Ivy covers the plan of treatment from the front lines to the surgical hospital where a maxillofacial team consisting of a surgeon and a dental surgeon trained in this type of work are stationed. Points demanding special attention in the combat area have been listed as (1) arrest of hemorrhage, (2) provision of adequate respiratory airway, (3) temporary approximate reduction and fixation of bone fragments and (4) provision of safe transportation from the combat zone to a hospital in the rear.

Arrest of hemorrhage as a general rule may be accomplished by pressure from a gauze pack; but for hemorrhage from larger vessels the use of clamp and ligature may be required. In patients with respiratory embarrassment it is suggested that with loss of control of the tongue, as in an unconscious patient, a long suture be placed through its tip so that it may be brought forward and attached to the dressing.

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75. Mowlem, R.; MacGregor, A. B.; Buxton, J. L. B., and Barron, J. N.: External Pin Fixation for Fractures of the Mandible, *Lancet* 2:391-393 (Oct. 4) 1941.

76. Ivy, R. H.: First Aid and Emergency Treatment of Gunshot Wounds of Jaw, *Mil. Surgeon* 89:197-201 (Aug.) 1941.

With excessive swelling of soft tissues a rubber tube may be inserted through the nose or the mouth to the nasopharynx. Tracheotomy should be used only as a last resort.

The approximate reduction and fixation of fragments will be dependent on whether a dental surgeon is available. The preservation of all comminuted viable fragments of bone which may be used in the final reconstruction procedure is stressed. A simple emergency splint may be constructed by the use of two or three tongue depressors secured to the frontal region, extending down in front of the chin, and to this may be attached a ligature wire which has been passed through the lower front teeth or around the chin segment of the mandible, thus preventing backward displacement. In case of fracture of the upper

*Results of the Treatment of Compound Fractures in Jackson's Series of Cases*

Type of Treatment	No. of Cases	Pyogenic Infections		Gas Bacillus Infections		Secondary Amputations		Number of Deaths	No. of Cases in Which Internal Fixation Was Used	Average Hospital Stay, Days
		No.	Per Cent	No.	Per Cent	No.	Per Cent			
1. Debridement.....	50	27	54	5	10	5	10	3	0	37.7
				Two treated with x-ray and recovered; two died; one amputation with recovery						
2. Debridement and prophylactic x-radiation..	57	9	15.8	0		0		0	0	19.8
3. Debridement, prophylactic x-radiation and oral sulfanilamide.....	16	7	43.7	1	6.2	0		1	0	22
4. Debridement and local implantation of sulfanilamide.....	54	3	5.6	0		0		0	11	6.8

jaw this may be attached to the upper teeth in a similar manner. The safe transportation from the combat zone to the hospital for the final definite treatment should be the same as for any other type of injury, except that semiambulant patients do better if permitted to sit up. If recumbency is necessary, the prone position is most desirable.

[ED. NOTE: This detailed discussion of first aid and emergency treatment should be read by every medical officer who in the present conflict may be assigned to duty in the combat zone.]

*Compound Fractures.*—Jackson<sup>77</sup> reviews the types of treatment for compound fractures. Her whole article is summed up in the table herewith presented and the statement that local implantation of sulfanilamide in compound fractures after debridement marks the greatest progress in the history of the treatment of compound fractures.

77. Jackson, R.: Comparative Study of Treatment of Compound Fractures, South. M. J. 34:319-323 (March) 1941.

Stich<sup>78</sup> gives a brief historical résumé of the methods of treatment of gunshot wounds of the knee and the lower extremities, stating that the best results have been obtained by aseptic dressings and immobilization in plaster. Of particular interest in the historical discussion is the information that during the Revolutionary War 837 of 1,000 patients with gunshot injuries of the knee died. The author adds to the emergency care the injection of 0.5 per cent procaine hydrochloride into the wound from a normal skin area as a method of treating shock. He also injects from 40 to 60 cc. of prophylactic antigas bacillus serum into the muscles about the site of injury. Only in large wounds of the joints without much destruction of bone does he recommend excision of the outer wound and closing the skin and eventually the capsule with a few wide sutures. In the majority of gunshot fractures thorough debridement is possible up to twelve hours, but suturing is contraindicated. The author does not recommend cod liver oil dressing of fresh war wounds even after a careful wound toilet. In cases in which the wound is left wide open, suturing may be done after a few days if there is no fever and the patient is somewhat restored.

Progress since 1860 in the treatment of open fractures is shown by the facts that Bilothe reported 219 cases occurring between 1860 and 1867 with a mortality rate of 68.8 per cent and amputations in 20 per cent, that at the Zurich Clinic between 1899 and 1929 there were 675 cases with a mortality rate of 14.9 per cent and amputations in 18.5 per cent and that Böhler and Ehalt reported 307 cases occurring up to 1937 with a mortality rate of 3.5 per cent and amputations in 4.58 per cent.

Wallis and Dilworth<sup>79</sup> have used sterile gauze dressings soaked in 12 per cent solution of lactose to pack into the wounds of compound fractures and chronic osteomyelitis. It is stated that since bacteria prefer to feed on sugar rather than on proteins there is less putrefaction. They report less odor during the Orr treatment and no impairment in healing. The dressings do not become adherent to the wounds. [Ed. NOTE: Some observers, however, report that the difference in odor with this treatment is not appreciable and that the gauze does stick to the granulation tissue. This is worth a trial by all surgeons treating infected wounds.]

Venable and Stuck<sup>80</sup> discuss the use of vitallium plates and the local implantation of sulfanilamide in the treatment of compound fractures.

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78. Stich, R.: Therapy of Gunshot Fractures of Extremities, *Med. Welt* **15**: 29-32 (Jan. 11) 1941.

79. Wallis, A. D., and Dilworth, M. J.: Lactose for Prevention of Odors in Closed Cast Treatment of Compound Fractures, *Brit. M. J.* **1**:750-751 (May 17) 1941.

80. Venable, C. S., and Stuck, W. G.: Use of Vitallium Appliances in Compound Fractures, *Am. J. Surg.* **51**:757-766 (March) 1941.

They do not advise this as a routine procedure. Formerly they allowed compound wounds to heal by scar tissue which bound the skin to the bone; now they apply the plates through a clean incision away from the contaminated area and treat the compound wound separately. They conclude that vitallium is a safe metal to place in compound fractures when used in this manner. They further report in a study of 1,227 patients with fractures of all types, including compound, treated by sixty surgeons with vitallium appliances that 92.6 per cent gained solid union, 3.8 per cent showed delayed union and 3.6 per cent ended in nonunion (reportedly not the fault of vitallium). [ED. NOTE: This is evidence in favor of the mechanical fixation of bad compound fractures when combined with chemotherapy.]

Pulaski and Chandlee<sup>81</sup> report on zinc peroxide in the treatment of compound fractures and traumatic amputations. They state that zinc peroxide not only has a "continuous inhibiting effect on the hemolytic streptococcus, the gas gangrene organisms, and other anaerobic bacteria, but has as well bactericidal and detoxifying action." It has no general toxicity or local irritation. The wounds were flooded with freshly prepared zinc peroxide after a thorough debridement. Internal fixation was used sometimes. The zinc peroxide used must be a reliable preparation. It should be used as a suspension creamy enough to reach every part of the wound and should be kept wet since moisture is necessary for the liberation of oxygen. It is not absorbed and should not be used in closed wounds. The results in 18 cases (10 were cases of injuries of the phalanges) were sufficiently encouraging to warrant continuing the use of zinc peroxide prophylactically in the prevention of infection in fractures. [ED. NOTE: This method apparently did not receive a thorough test by the authors in treatment of severe compound wounds, i. e. those of the tibia and the femur.]

*Experimental.*—Caldwell<sup>82</sup> produced the counterpart of a compound fracture in the femur of guinea pigs and infected the wounds with a lethal number of *Clostridium welchii*. Debridement of the wounds followed by implantation of 15 to 30 mg. of sulfanilamide crystals and closure resulted in survival of only 4 of 19 animals (all controls died). Debridement and irrigation of similar wounds left open and followed by the administration of 50 mg. of sulfanilamide intraperitoneally every six hours allowed survival of 7 of 9 animals (8 of 10 controls died). Debridement and irrigation of such wounds followed by implantation of zinc peroxide paste and suture of the wounds resulted in the survival

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81. Pulaski, E. J., and Chandlee, B. H.: Zinc Peroxide in Treatment of Compound Fractures and Traumatic Amputations: Report of Eighteen Cases, *Surgery* 10:904-916 (Dec.) 1941.

82. Caldwell, G. A.: Treatment of Gas Gangrene Experimentally Produced, *J. Bone & Joint Surg.* 23:81-85 (Jan.) 1941.

of 4 of 5 animals. Similar wounds sutured and treated with roentgen therapy in varying doses (100 to 200 r one to three hours after inoculation) resulted in the death of 7 of 10 animals (all controls died), and the wounds of the surviving animals healed with dry necrosis of the skin and deep sloughing in the muscle layers. The author concludes from these experiments that the intraperitoneal use of sulfanilamide and the implantation of zinc peroxide into the wound are most efficacious and that of the two zinc peroxide is more satisfactory. [ED. NOTE: This is excellent experimental evidence of the value of sulfanilamide crystals and zinc peroxide paste in infected wounds.]

*Fracture Teaching.*—Murray<sup>83</sup> calls attention to the excellent work done in the past several years by the Committee on Fractures and Other Traumas of the American College of Surgeons. It is carried on through the activities of the various regional subcommittees of the American College of Surgeons. He further states that however good this effort has been it has been markedly inadequate. He calls attention to the fact that many medical students receive inadequate instruction in fracture training and that this is not greatly improved in the intern years. This is of particular importance since it is well known that the average fracture is treated not by the fracture specialist but by the general practitioner, whose sum total of training in fractures consists of what he has acquired in medical school and during an ordinary internship without special education along the lines of traumatic surgery. This being the case, it is especially important that the fracture service be well organized, that the student be given an opportunity to examine the fractures at first hand and even to take part in their treatment and particularly that the intern in the hospital be permitted to observe fractures under the close supervision of a well trained fracture surgeon. Murray points out that the treatment of fractures is as much a part of general practice as the treatment of obstetric conditions or pneumonia but that education is much deficient with regard to the treatment of fractures whereas it devotes considerable attention to the treatment of these other conditions. In summation he makes a plea for the following measures: (1) instruction in the correlation between the pathologic nature and the repair of fractures and the symptoms and the indications for treatment of fractures; (2) correlation between the diagnosis and the treatment of fractures and the gross anatomic characteristics; (3) instruction in the basic principles underlying all fracture treatment, preferably by demonstration on actual patients; (4) adequate follow-up of actual patients from the time of reduction of the fracture until the end result is obtained; (5) opportunity

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83. Murray, C. R.: Undergraduate Education in Fractures and Other Traumas, Surg., Gynec. & Obst. **72**:399-401 (Feb., no. 2 A) 1941.

to see late results on similar patients; (6) actual instruction and practice in application of the Keller-Blake and Murray-Jones traction splints; (7) some organized training in first aid and the treatment of trauma, preferably in the sophomore or junior years. [ED. NOTE: This is an excellent discussion and a timely plea for more active training in the treatment of trauma, particularly emphasizing the fact that undergraduate education in this respect has been incomplete and must be improved.]

*Operative Fixation of Fractures.*—Murray<sup>84</sup> presents material and conclusions reached by the fracture service of the Presbyterian Hospital and Sloane Hospital for Women, New York, in the treatment of approximately 13,000 fractures, over 600 of which were treated by open reduction. He attempts to give an evaluation of the relative advantages of primary operative fixation and the so-called close reductions. He immediately divides the patients with fractures into two groups: In the first group are those patients who must be operated on because of necessity, i. e. (1) those with fixed interposition of tissue between the bone ends; (2) those in whom adequate reduction has not been secured by conservative methods; (3) those whose fractures experience has shown require operative reduction; (4) those with soft part injuries, and (5) those with compound fractures. He eliminates this group entirely from the discussion. The second group are those in which primary operative reduction is selected as the method of choice, although conservative treatment has been considered. He considers four questions of vital concern and answers them in some detail. The four questions are: (1) What are the theoretic advantages of open fixation? (2) Can advantage be taken of these theoretic advantages without undue risk to the patient? (3) What conditions are essential to carrying out the operation? (4) How can these conditions be established in any given institution?

In answering the first question he covers the problem by stating that the ideal reduction would be one in which the fragments went together without trauma and in which they were held adequately, permitting immediate function. Obviously, this cannot be carried out completely in any method. The disadvantages of the closed method are prolonged immobilization and frequent inadequacy of reduction, resulting in lesions of the soft parts incident to forced manipulation. The same disadvantages apply to a lesser extent when pins or wires are used and incorporated with plaster. Traction-extension methods may cause a minimum of tissue damage but often do not result in good reduction and also permit only incomplete immobilization of the joint. There is likewise the additional risk of infection, which with proper technic

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84. Murray, C. R.: Primary Operative Fixation in Fractures of Long Bones in Adults, *Am. J. Surg.* **51**:739-747 (March) 1941.



should be minimal. He concludes that operative fixation is the only method which simultaneously provides atraumatic anatomic reduction with coincident abolition of a large part of the pathologic processes in the tissue, rigid fixation of the fracture and extremely early and full mobilization of the extremity involved.

The second question he answers by saying that these theoretic advantages can be used in a practical manner, as has been demonstrated in his own clinic. He names certain fractures, namely, those of both bones of the leg, those of the femur and those of the humerus. These resulted in: (1) better anatomic results; (2) fewer long-standing disabilities; (3) shortening of convalescence; (4) increased speed in healing time, as shown by roentgen examination and less delayed union and nonunion. The technic has been perfected to the point where the contraindications to be considered are: (1) the patient as an operative risk; (2) the skin conditions, and (3) the features of the fracture itself which make it doubtful that it can be fixed by rigid fixation.

In answer to the third question he insists that operation should be done within a few hours. The most rigid operative technic is of course essential to minimize the danger of infection. Further, it is necessary to get absolute accurate reduction without trauma, rigid fixation with strong internal fixation material and fixation in two planes to prevent torsion. This demands all of the meticulous care such an apparatus requires and early weight bearing with the extremity protected by a well fitted brace with the patient instructed adequately in its use.

In answer to the fourth question he says that it is absolutely essential that there be close cooperation between the doctor and the institution. It is of course essential that the surgeon be well trained in this technic and that he use it with care. It is equally important that the equipment of the institution provide the facilities not only for operation but for after-care.

Murray's conclusion is that, given these cooperative circumstances, these theoretic advantages can be safely translated into practical benefit to the patient sufficient to justify the use of the method under certain definite conditions. He emphasizes particularly that if these certain specific conditions cannot be met primary operative fixation is not the method of choice and that some conservative method should be adopted.

[ED. NOTE: This is a comprehensive discussion of this problem by one who is convinced that primary operative fixation is the treatment of choice. Many surgeons will find great difficulty in fulfilling all the requirements he mentions. However, Murray certainly has proved his case and by virtue of the exacting conditions he lays down has demonstrated also that use of these methods must of necessity be limited to a rather select group of surgeons and institutions.]

*Obstetric Fractures.*—Grossman<sup>85</sup> discusses various types of fractures of the newborn including the rather common fractures of the femur and the clavicle and the rather uncommon fractures of the humerus, the tibia and the fibula. He is of the opinion that the majority of these result from intrauterine manipulation of the child. He emphasizes the fact that they heal promptly with massive callus. The major complication to be feared is involvement of the skin by undue pressure. The prognosis is uniformly good.

*Parachute Injuries.*—Tobin, Cohen and Vandever<sup>86</sup> in a preliminary survey of injuries sustained during the first year of parachute jumping find that in 4,490 parachute jumps there have been a total of 121 injuries, 2.4 per cent. Thirty-two of the patients in this group were injured severely enough for admission to the hospital. Seventy-eight per cent of the patients admitted had fractures. Malleolar injuries totaled 40 per cent, while injuries of the tibia and the fibula constituted 8 per cent and injuries of the lateral condyle of the tibia represented 4 per cent. There was only 1 fracture of the os calcis; this was complicated by fractures of the scaphoid, the cuboid and the metatarsals. One anterior dislocation of the hip joint occurred owing to the violent wrenching of the parachutist's harness when the emergency chute was opened after he had remained suspended to the tail of the plane for approximately ten minutes. The remaining fractures were of relatively minor nature, 16 per cent being of the metatarsals and the phalanges.

The authors have reviewed all of the available foreign literature and classify the injuries into four major groups, as suggested by René de Gaulejac: (1) injuries resulting in death occurring as a result of entanglement with the plane or crashing to the earth when the parachute failed to open; (2) abdominal thoracic injuries with or without nervous or vascular complications produced by the shock of the opening of the parachute; (3) various organic lesions developing during the third phase of the jump, i. e. after the parachute had opened; (4) the more or less complicated injuries of the lower extremities resulting during the fourth phase of the jump as a result of contact with the earth.

There was a decrease in the percentage of the injuries during the last month of parachute jumping. This was attributed to improved methods of preliminary training which constitutes ground training with jumps from platforms of 4 to 6 feet (121.92 to 182.88 cm.) and from towers 250 feet (76.2 meters) high in an open parachute. The conditions simulate exactly a jump from a plane. In this preliminary training the student is taught the method of landing in order to take up shock. He is instructed to land on the balls of both feet, which should be shoulder

85. Grossman, J.: Fractures in Newborn, *M. Rec.* **153**:85-87 (Feb. 5) 1941.

86. Tobin, W. J.; Cohen, L. J., and Vandever, J. T.: Parachute Injuries, *J. A. M. A.* **117**:1318-1321 (Oct. 18) 1941.

width apart. He should fall forward in a roll so that the shock may be broken at the knees and the ankles.

*Procaine Hydrochloride Technic in the Treatment of Fractures.*—Ferguson and Erb<sup>87</sup> discuss in some detail the rationale of the proper selection of cases and outline the results of injecting procaine hydrochloride and using early mobilization in the treatment of non-weight-bearing fractures. In discussing the theory they credit Leriche with the best rationalization of the effect of procaine hydrochloride; which is briefly that the swelling and edema caused by the trauma is the result of a secondary vasospasm which is an axon reflex. This can be interrupted either by injection into the sympathetic ganglion or by local injection around the site of the injury. According to this theory the relief of pain is due not to the anesthetic effect of the procaine hydrochloride but to the relaxation of vasospasm which in turn reduces the edema and swelling of the part. The authors feel that this plays an equal part with mobilization, since mobilization alone in many instances does not relieve pain. On the other hand, mobilization is of extreme value, particularly in the region of joints since it permits joints to accommodate themselves to whatever irregularity has been caused by the fracture. Their method is simple; 1 or 2 per cent procaine hydrochloride without epinephrine is injected into the point of maximum tenderness until the tenderness entirely disappears. If this occurs after eight to twelve hours, another injection is given and may be repeated as often as the pain recurs. The authors stress the fact that it is not always advisable to begin mobilization immediately, although this should be begun as early as possible. If there is extreme swelling of the area before treatment, it may be necessary to wait a few days for this to subside before mobilization is begun, although injection is carried out immediately. They point out also that the weight-bearing bones of the lower extremity, or those in which immobilization is required to maintain reduction, are not suitable for this method. They bring out also the fact that the efficacy of therapy does not rely alone on this relief of pain but that it permits the patient to begin to resume his normal activity much more rapidly than with the older type of treatment by external fixation. They report 84 cases in 80 of which treatment consisted of injection of procaine hydrochloride and early mobilization. The majority of the fractures were about the ankle, the tarsus and the metatarsus, the phalanges, the upper part of the humerus, the elbow, the metacarpals and the wrist. A detailed discussion is given of each group. In conclusion, they point out:

Many minor fractures are best treated by early mobilization and procaine injection. The procaine injection at the site of fracture or into the sympathetic

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87. Ferguson, L. K., and Erb, W. H.: *Procaine Injection and Early Mobilization in Non-Weight Bearing Fractures*, Ann. Surg. **114**:293-308 (Aug.) 1941.

ganglia interrupts the reflex which produces vasomotor changes, edema, and pain at the injured site. Early mobilization is thereby permitted, and rapid and excellent fracture healing results. The period of disability is reduced and the eventual end-result is improved in many instances, especially in articular fractures. . . . Only fractures which do not require reduction in non-weight-bearing bones can be treated by this method.

[ED. NOTE: This is a thoroughly stimulating discussion of this subject and in our opinion is presented with the sanest outlook and the least prejudice of any of the many articles on this subject which have appeared in the literature. The authors have analyzed their results carefully and have wisely refrained from attempting to apply this method to every type of fracture. It is worthy of considerable study.]

## II. FRACTURE DEFORMITIES

*Fracture Healing.*—Physiologic and pathologic processes of bone metabolism with particular reference to chemical and biochemical factors in demineralization and bone growth have been the subjects of articles during the past year. Experimental and clinical data have been correlated, but no fundamental advance has been achieved in this field.

Urist and McLean<sup>88</sup> present microscopic studies of the healing process of fractures of fifteen litters of normal rats and describe the steps of fracture healing as it probably occurs under optimum conditions.

The first reaction to injury is sterile inflammation associated with trauma and hemorrhage. The bone defect is filled and surrounded by extravasated blood and inflammatory exudate. The reparative process begins with the formation of connective tissue (fibrocartilaginous callus) which differentiates into hyalin and fibrocartilage. While this process is taking place, new bone formation begins under the periosteum and endosteum at some distance from the fracture site. This new bone progresses and invades and replaces the fibrocartilaginous callus, and this results in bony union.

Calcification begins in the new bone matrix formed subperiosteally and subendosteally and progresses toward the fracture site as quickly as the new bone matrix is formed. This matrix is calcifiable as soon as it is recognizable as osseous tissue. The matrix of hyaline cartilage becomes calcifiable when the adjacent cartilage cells become vesicular or hypertrophic. Only tissues recognizable as bone matrix or cartilage matrix calcify, and of this matrix only that in contact with the invading bone calcifies in the final callus.

Urist and McLean extended their studies of normal callus formation to observation of the effect of phosphate and vitamin D on the control

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88. Urist, M. R., and McLean, F. C.: Calcification in Callus in Healing Fractures in Normal Rats, *J. Bone & Joint Surg.* **23**:1-16 (Jan.) 1941.

of callus formation in rachitic rats. They found that in the rachitic rats the healing of fractures begins as it does in normal rats with the important difference that the healing process proceeds in the complete absence of calcification of the newly formed tissues for the first ten to fifteen days following the injury.

In the normal animal about the fourth day the intramembranous bone formed under the periosteum and endosteum has gained contact with the fibrocartilaginous callus, and its removal and replacement by bone are well under way.

In the rachitic animal there is a lag in the replacement of callus tissue by the newly formed osseous tissue, often until the ninth to twelfth day; this corresponds to the delay in calcification at the epiphysial line.

Calcification in the osteoid of the callus as well as in the epiphysial cartilage may be initiated by a single dose of phosphate. A diet inadequate in phosphate but supplemented by vitamin D does not produce rickets or manifestations of the absence of calcification at the fracture callus.

In connection with experimental work on the effect of estrogenic substances on callus production, Pollock and Ghormley<sup>89</sup> noted certain changes in the bone tissues distant from the fracture site which appeared to be of sufficient interest to warrant further study. It was demonstrated that the periosteum of the fractured humerus in the rat underwent stimulation and thickening not only in the area adjacent to the fracture site but all the way to the surgical neck. The authors state that this appeared to be the result of a general stimulation rather than the result of local trauma.

Hills and Weinberg<sup>90</sup> observed the effect of estrogen therapy clinically in 3 cases of delayed union or nonunion in fractures. Their conclusion is that callus formation in these cases was definitely influenced favorably by the use of estrone (theelin).

The results of their efforts to substantiate this clinical observation by experimental work on dogs and cats were not so striking as they anticipated. However, the authors feel justified in concluding that 9 of 13 cats and 6 of 7 dogs showed earlier and more abundant callus formation under estrogen therapy.

[ED. NOTE: None of the data published during the past year relating to the effect of estrogen therapy on the healing of fractures alters the conclusion drawn from previous publications, viz., that the administration of estrogens or any other endocrinotherapy has no practical

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89. Pollock, G. A., and Ghormley, R. K.: *Early Repair of Bone: Experimental Study of Certain Factors*, *J. Bone & Joint Surg.* **23**:273-279 (April) 1941.

90. Hills, R. G., and Weinberg, J. A.: *Influence of Estrin on Callous Formation*, *Bull. Johns Hopkins Hosp.* **68**:238-247 (March) 1941.

effect on the healing of fractures. The problem of nonunion still appears to be more local than constitutional.]

Murray,<sup>91</sup> basing his conclusions on the practical data gained by the intensive research of the last quarter of a century, notes the nature of the tissue reaction following fractures and states that the time and the method of treatment should be based on an understanding of the physiologic and pathologic tissue conditions present.

The chronologic time at which the various stages of tissue repair occur varies considerably in each individual patient. Hence time as gaged by hours or days means little except in establishing an average. Time refers to the stage of progress the pathologic condition has reached. It is to be interpreted in terms of clinical evidence, such as the character and the extent of swelling, pain, tenderness, edema, infiltration and ecchymosis. The logical rule to follow is to treat the fracture in accordance with the pathologic condition present, regardless of chronologic time elapsed since injury, by modifying whatever method the surgeon is best capable of handling effectively.

The influence of the timing of the process on the choice of method is illustrated by the author's citations of his clinical conclusions based on the results observed in twelve years' experience in a large fracture service conducted on the aforementioned principles.

The time schedule of the development of tissue reaction after fracture dictates the technic of traction-suspension as a method of treatment. Reduction, so far as length is concerned, should be attained as early as possible, preferably in the first four hours, before the muscles have begun to lose their elasticity from infiltration. Overpull is safe before muscle fixation has occurred but should be avoided afterward.

Open reduction of fractures requiring this procedure is best done within the first four to eight hours after injury. During such an early operation the escape of blood and exudate from the tissues leads to a minimal soft part lesion with its functional implications and on the basis of the author's conception of the healing process to more certain and quicker calcification of the healing tissue to form callus.

The least satisfactory time for open reduction of a fracture is between the twelfth and the twenty-eighth day.

Recent fractures treated by open reduction followed by cast immobilization take longer for bone healing than similar fractures treated by closed methods. This is particularly true if the operation is done some days after the healing processes have started. To the pathologic process already fixed in the tissues is added the damage of operative trauma. Early emergency operation with internal fixation rigid enough

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91. Murray, C. R.: Timing of Fracture-Healing Process: Influence on Choice and Application of Treatment Methods, *J. Bone & Joint Surg.* **23**:598-606 (July) 1941.

to allow active mobilization postoperatively in counterbalanced suspension not only restores joint and muscle function more promptly but promotes the speed and certainty of fracture healing.

From the points just mentioned it is obvious that the principles of reduction as soon after the injury as possible are applicable to all methods of reduction.

It is the author's belief that students can derive a more sound understanding of the basic principles which underly fracture treatment as a whole if they think more of what any method of treatment accomplishes in guiding the pathologic process after treatment and less about the technical details of each method. The ability to interpret physical signs as indicative of the pathologic state present and of the speed with which it is progressing is a sound basis for the intelligent use of any method of treatment.

*Pseudofractures.*—Camp and McCullough<sup>92</sup> present a comprehensive review of the various conditions exhibiting pseudofractures. Pseudofractures may be described as transverse zones of rarefaction varying in width from less than a millimeter to more than a centimeter. They are frequently mistaken for true fractures, and since in reality they are generally an indication of certain weaknesses or dysfunction of the skeletal system, it is important that their true character be identified.

They have been reported by various authors under a variety of names, such as pseudofractures, Looser's zones, multiple spontaneous idiopathic symmetric fractures, osteoporosis myelolytica, insufficiency fractures and march fractures. The authors state that none of these conditions constitute a clinical entity but are simply a manifestation of excessive strain either of normal or of weakened structure.

Pseudofractures occur in a variety of diseases which have no relation to each other. Studies of Looser of the nature of these defects in association with osteomalacia and rickets stimulated wide interest in these subjects during the food shortage in Europe following the first World War.

Roentgenographically these skeletal defects show three different forms: (1) those associated with certain malacic diseases, which may appear as small subperiosteal notches in the cortex and which progress across part or all of the cortex as a band of decalcification without disturbance in the continuity of the bone; (2) those lesions not associated with malacic diseases, which may be revealed as cracks or fissures extending through the cortex on one side, usually the convex side, of pathologically curved bones; (3) those lesions which appear as fusiform callus formations only, no crack or decalcification being apparent roent-

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92. Camp, J. D., and McCullough, J. A. L.: Pseudofractures in Diseases Affecting Skeletal System, *Radiology* 36:651-663 (June) 1941.

genographically (these lesions seem to be identical with the so-called march fracture).

[ED. NOTE: Exception must be taken to the statement that this third type consists entirely of a fusiform callus without a fracture in the cortex. March fractures, which are a typical example of this type, will regularly show a fracture line if serial roentgenograms are taken.]

Pseudofractures are most commonly found in the tibia, the forearm, the pelvic bones, the metatarsal bones, the ribs, the radius and the ulna.

In many cases the condition is associated with hunger osteomalacia, rickets or late rickets. In other cases it occurs in normal bones after unusual strain or repeated minor strains. In the latter cases it resembles the breaking of a wire by multiple minor cracks resulting from repeated bending.

Biopsy and microscopic studies of these fracture lines have not demonstrated any unusual pathologic condition. Honigmann and the authors found only increased lacunar absorption and the development of meshlike bone without calcification. Studies of the blood chemistry showed only those variations which might be expected with the underlying disease.

Macey<sup>93</sup> reports a single case of multiple pseudofracture with absence of phosphatase activity in the blood serum.

After a review of the voluminous literature covering the subject, Camp and McCullough conclude that pseudofractures do not represent a disease entity but that they are partial fractures due to excessive strain, which may take several forms, depending on the associated pathologic condition and on the nature of the excessive strain.

Nagura,<sup>94</sup> reporting the microscopic picture of the so-called transformation zones of Looser, says that he observed the area to be composed of an embryonic type of callus formation, both cartilage and fibrocartilage, on both sides of which osseous transformation was taking place. The zones represented an area of interrupted continuity about which reconstruction of bone was taking place. Similar zones of rarefaction have been found in osteochondritic diseases, such as König's and Perthes' disease.

*Post-Traumatic Osteoporosis.*—Herrmann and Caldwell<sup>95</sup> review the clinical and roentgen manifestations of acute post-traumatic osteo-

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93. Macey, H. B.: Multiple Pseudofractures: Case (with Absence of Phosphatase Activity of Blood Serum), Proc. Staff Meet., Mayo Clin. **15**:789-791 (Dec. 11) 1940.

94. Nagura, S.: Nature of So-Called Transformation Zones (Looser): Cartilage Callus Zones, Zentralbl. f. Chir. **67**:1971-1975 (Oct. 19) 1940.

95. Herrmann, L. G., and Caldwell, J. A.: Diagnosis and Treatment (Including Periarterial Sympathectomy) of Post-Traumatic Osteoporosis, Am. J. Surg. **51**:630-640 (March) 1941.



porosis and clearly distinguish it from the osteoporosis of disuse. They agree with the concept of Nobel and Hauser that the only theory which can satisfactorily explain all the pathologic physiologic characteristics of bone in true osteoporosis is that the disturbance is a manifestation of trophoneurosis as originally suggested by Kienböck in 1901.

Treatment by the ordinary conservative means, such as physical therapy and active mobilization, have only slightly reduced the period of pain and dysfunction. Roentgen therapy, as advised by Mumford, has reduced the pain but has not materially shortened the period of disability or the final permanent loss of function.

The authors recommend periarterial sympathectomy and report the results in 34 cases of the acute painful variety treated by this method. All of the patients had relief of the severe pain within twenty-four hours with disappearance of edema and functional disturbance within a few days. The period of disability averaged three months in this series, while for those previously treated by nonoperative measures it was nine months.

The operation should be performed during the acute stage of the disease, since it is not successful in the subacute or chronic stage.

Carpinteri<sup>96</sup> reviews Sudeck's theory of acute post-traumatic bone atrophy. He then points out the practical conclusions to be drawn and summarizes them as follows:

1. Local injury to the bone causes a general skeletal reaction stimulating the phosphate-esterase capacity of all skeletal parts, which acts as a physiologic homogeneous organic system under these conditions as during growth.

2. Every injury, independently of its destructive effect, constitutes a direct injury to the mobility of the vessels leading to genuine active hyperemia.

3. The diminution of the density of shadow of a bone, far from indicating atrophy, is evidence of an intense process of ossification, and increased density indicates dying bone or eburnation.

4. Therefore, what Sudeck earlier described as acute bone atrophy constitutes only an accelerated metabolism in the bone. As the only reaction of the bone to various pathologic factors consists in loss of heavy salts, the radiologic manifestation of the syndrome must be designated as haliteresis.

*Aseptic Necrosis of Cancellous Bone and Its Relation to Fractures.*  
—In a comprehensive monograph Bozsán<sup>97</sup> correlates the historic and

96. Carpinteri, E.: Significance Modality and Roentgen Picture of Sudeck's Acute Atrophy, *Gior. di med. mil.* **88**:750-771 (Oct.) 1940.

97. Bozsán, E. J.: Compression of Cancellous Bone, Principal Manifestations in Head and Neck of Femur: Treatment by Connecting Drill Channels, *Am. J. Surg.* **53**:537-618 (Sept.) 1941.

the pathologic data relating to that group of diseases showing nutritional or growth disturbances in the head of the femur and the adjacent structures. This group includes such conditions as Legg-Calvé-Perthes disease, osteochondritis dessicans, epiphysial separation of the femoral head, malum coxae senilis and aseptic necrosis of the femoral head following fracture.

The author states that he has found an explanation that solves the question of the underlying cause of aseptic bone necrosis, and he explains on this basis the causation and the pathologic nature of all the related pathologic processes known under the various disease classifications already listed. The characteristic wedge-shaped areas of aseptically necrotic bone may be produced by a mechanism other than infection, namely, compression of a spherical wedge-shaped portion of cancellous bone.

The results of compression applied to a spherical-shaped body composed of cancellous material demonstrate: (1) that the compressed area is cone shaped; (2) that the compression does not damage the whole substance of the cone but is most effective on the jacket of it; (3) that within its compression pattern secondary component wedges are demonstrable, each impact producing its own wedge, and (4) that changes in the curvature of the surface and the speed of force alter the shape of the compression pattern.

By correlating these observations with the fact that all the diseases under consideration occur in cancellous bone and at places where the bone presents a more or less spherical surface, the author arrives at the concept of compression of cancellous bone, which he is convinced is the sole cause of all of these diseases and may be considered an entity because while manifest in a variety of clinical pictures it presents at all times the same pathologic features.

If cancellous bone is subject to a force which is greater than its maximum of structural strength, its structure will collapse, this collapse obeying the laws of mechanics. The minute girders of the cancellous structure break, and these broken trabeculae interrupt the blood supply to the inclosed cone. The necrosis thus produced is mechanical and not due to an embolus of a terminal artery entering the apex of the cone as presumed by Axhausen.

The parts of the skeleton that harbor these diseases contain, besides cancellous bone, also cartilage, particularly in childhood and adolescence. Cartilage is fundamentally different in its physical properties from cancellous bone and hence does not suffer the same effects from compression. The relative amounts of cartilage and bone present at the different age periods explain the different clinical forms observed in children and in adolescents.

Lagomarsino and Muscolo<sup>98</sup> describe a case of aseptic necrosis of the head of the humerus after a fracture-dislocation in which the roentgen and clinical pictures resembled that of aseptic necrosis of the femoral head following central fractures of the neck. In this case the aseptic necrosis of the humeral head was demonstrated by roentgen examination about ninety days after the injury. The condition progressed slowly, causing a disappearance of more than half of the epiphysis in a period of sixteen months.

[ED. NOTE: Aseptic necrosis of the humeral head has never been observed by one of us (J. S. S.), nor has this editor seen it described before in the literature. The age of this patient is not given in the abstract. An epiphysial disturbance during the growth period must be considered.]

There has been and still is considerable difference of opinion as to the best method of treatment for fractures of the carpal scaphoid.

Geissendorfer<sup>99</sup> states that conservative methods of immobilization in old fractures of the scaphoid have not proved successful. Surgical removal of the smaller fragment after nonunion has occurred is not satisfactory since a painful wrist usually persists. Drilling operations, as described by Beck and Schnek, have given some good results, but the author does not think this method provides the immobilization necessary to obtain union. He recommends nailing the fragments with a Kirschner nail and reports union with good results in 6 cases of old carpal scaphoid fractures. Complete immobilization is maintained in a cast for three months after operation.

Massart and Leger<sup>100</sup> recommend drilling of old scaphoid fractures after visual exposure of the fragments. They do not recommend more than one week's immobilization.

[ED. NOTE: The whole problem is still somewhat confused, chiefly because no one has had an opportunity to study the effects of various forms of treatment in any large series of cases, particularly in cases of acute fracture. The diagnosis is frequently overlooked in the acute stage because of inadequate roentgen examination or because fracture lines exist at the time of acute injury which cannot be seen in roentgenograms but which become apparent later after bone atrophy and absorption at the fracture site have taken place. This has been observed by one of us

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98. Lagomarsino, E. H., and Muscolo, D. T.: Aseptic Necrosis of Head of Humerus After Its Fracture-Luxation, *Arch. urug. de med., cir. y especialid.* **17**: 450-457 (Oct.) 1940.

99. Geissendorfer, H.: Successful Therapy of Old Fractures of the Carpal Scaphoid with Nailing, *Zentralbl. f. Chir.* **68**:343-346 (Feb. 22) 1941.

100. Massart, R., and Leger, L.: Therapy of Painful Pseudoarthrosis of Carpal Scaphoid by Beck Operation, *Mém. Acad. de chir.* **66**:505-510 (May 1-8) 1940.

(J. S. S.) both in cases of fracture of the carpal scaphoid and in cases of central fracture of the femoral neck. In general the problem appears much the same in these two types of fractures for the following reasons: 1. Complete immobilization by external appliances is difficult and is usually not obtained. 2. Union occurs entirely by endosteal callus, the formation of which is prevented by slight movement at the fracture site. 3. The blood supply to the fragments is inadequate. 4. Aseptic necrosis of one fragment is frequent, and this interferes further with union. While union may be obtained in many cases of fracture of the carpal scaphoid by external immobilization alone (as was accomplished by the Whitman method of treating central fractures of the femoral neck), it seems reasonable to expect that a corresponding increase of unions in carpal scaphoid fractures will take place if immediate internal fixation (providing adequate immobilization) is employed at the time of the acute fracture. Further use and reports of such treatment might be helpful.]

*Fractures of the Neck of the Femur.*—The *modus operandi* of union in fractures of the femoral neck has been the subject of much study and a voluminous literature.

Kulowski and Luck<sup>101</sup> were fortunate in obtaining the postmortem specimen of a fractured hip seven weeks after injury and six weeks after a satisfactory nailing with a Smith-Petersen nail. Their report of the microscopic study of the tissues at and adjacent to the fracture site, presumably at the height of activity in the healing process, is concise and informative. Grossly there was no evidence of periosteal callus. On frontal section of the specimen it was evident that an early stage of bony union had been obtained. The marrow of the capital fragment was fatty; all other marrow in the specimen appeared grossly hematogenous.

They report the microscopic examination of the fracture site as follows:

The most outstanding feature of the fracture site was the presence of a multitude of fine-caliber, short, narrow, smooth trabeculae, more than half of which were still in the osteoid stage. Osteoclasts were conspicuous for their paucity. A moderate number of small osteoblasts were attached to the surfaces of some of the trabeculae. Most trabeculae appeared to have formed on the basis of fibrous tissue. These small young trabeculae were aligned in all directions, with no respect for static lines of stress. A few large mature trabeculae were also present in the fracture zone. Many of these trabeculae were dead, presumably as a result of separation from their blood supply at the time of the fracture. New bone was

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101. Kulowski, J., and Luck, J. V.: Microscopic Changes After Internal Fixation of Transcervical Fracture of Femur, *J. Bone & Joint Surg.* **23**:17-22 (Jan.) 1941.

applied to the surfaces of numerous old trabeculae at and adjacent to the fracture site. A considerable degree of hyperaemia existed in the vessels of the fibrous marrow in this region. Marrow fibrosis was sharply limited to a zone approximately one-quarter inch wide at the fracture level. . . . Beyond this zone the marrow appeared quite normal. Not a solitary field of cartilage in any form could be found at the fracture site. The healing process appeared to consist simply of the formation of osteoid and bony trabeculae on the basis of reactive fibrous tissue which developed between the fragments and in adjacent marrow spaces.

The femoral head was viable and showed the same microscopic changes that have previously been reported.

The femoral neck and the trochanter revealed a good blood supply with viable trabeculae and marrow. There was no subperiosteal new bone or callus at or adjacent to the fracture site.

The authors conclude that if internal fixation is adequate the process of union by endosteal callus and bone formation is rapid and adequate enough to insure union much sooner than has been generally appreciated.

*Ununited Fractures of the Femoral Neck.*—The consensus of those who have given most thought to the problem of ununited fractures of the femoral neck is that no one procedure is suitable for use in all cases. Each case must be studied individually, and the various components as to the general condition of the patient and the local conditions of the fracture must be weighed before deciding which of several procedures appears most suitable.

Henderson<sup>102</sup> states that the ideal procedure is the restoration of bony union between the head and the neck in the normal anatomic relation. This is best accomplished by extra-articular osteosynthesis when conditions are favorable. He states that less than 10 per cent of ununited fractures of the femoral neck qualify for this procedure.

He describes the operative technic in which a fibular graft is used without other internal fixation and reemphasizes the previously published general and local requirements for the suitability of this operation. He reports 11 bony unions and 8 excellent results in 14 cases in which treatment was carried out by bone grafts.

Bickel and Ghormley<sup>103</sup> add 2 cases to those already reported of ununited fractures of the femoral neck successfully treated by the Brackett reconstruction operation. In both cases the femoral heads were viable, and no arthritic changes were present.

Several articles have appeared during the last year advocating the high type of osteotomy (McMurray) as the simplest and most

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102. Henderson, M. S.: Extra-Articular Osteosynthesis for Nonunion of Fracture of Neck of Femur, *Arch. Surg.* **42**:557-565 (March) 1941.

103. Bickel, W. H., and Ghormley, R. K.: Brackett Operation for Ununited Fractures of Neck of Femur: Report of Two Cases, *Proc. Staff Meet., Mayo Clin.* **16**:345-348 (May 28) 1941.

universally successful operation for ununited fractures of the femoral neck. Reich<sup>104</sup> reports the results in 26 cases in which this method of treatment was used. Osteotomy is indicated in all cases of nonunion in which the head was demonstrated roentgenologically to be viable. It is contraindicated in those cases in which there is definite aseptic necrosis or osteoarthritis of the ununited head.

The mechanical principle on which the operation is founded is that by shifting the upper end of the shaft medially directly under the femoral head the shearing force of weight bearing at the fracture site is eliminated or transformed into a direct weight-bearing thrust of the shaft against the femoral head.

The operative technic described by McMurray with the use of a wire for a guide was employed. The patients were immobilized in a cast for six weeks.

The functional and anatomic results were satisfactory in 22 of the 26 patients. In the average case the shortening is not increased over 1 cm., and in some cases there may be an actual lengthening. Union between the head and the neck occurred in every 1 of the 22 successful cases. At the time of last observation (the longest period since operation was five years) there was no evidence of secondary osteoarthritis or aseptic necrosis.

Jahss and Mintz<sup>105</sup> review 16 cases of ununited intracapsular fractures of the hip treated by high trochanteric osteotomy. There were 14 satisfactory results, 1 failure and 1 death. In 5 cases bony union of the neck fracture resulted, and in those remaining cases in which such union did not occur excellent functional results with regard to stability of the hip, relief from pain and adequate range of motion were obtained.

The authors state that osteotomy is applicable in cases of nonunion of short or long duration, regardless of the viability of the femoral head.

The operation may also be useful for fresh fractures in which satisfactory reduction cannot be obtained and for which internal fixation is therefore contraindicated.

The following possible technical errors at operation are listed: (1) incomplete medial displacement of the femoral shaft; (2) an acute angle of osteotomy, which is to be avoided; (3) wide abduction of the limb, which also is to be avoided; (4) too high a level of osteotomy, which will interfere with inward displacement of the shaft; (5) too low a level, which will result in excessive shortening.

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104. Reich, R. S.: Ununited Fracture of Neck of Femur Treated by High Oblique Osteotomy, *J. Bone & Joint Surg.* **23**:141-158 (Jan.) 1941.

105. Jahss, S. A., and Mintz, B. J.: Transverse Osteotomy in Ununited Fractures of Femoral Neck, *Bull. Hosp. Joint Dis.* **2**:143-153 (Oct.) 1941.

Early check of the position of the osteotomy and revision of the position if necessary are advised.

The usual residual shortening is about 1 inch (2.5 cm.), most or all of which was present before the operation.

Speed and Smith,<sup>106</sup> in an analysis of a series of 30 osteotomies, report results which compare favorably with those of reconstruction operations or bone grafts for osteosynthesis. In many of the early cases in this series the osteotomies were performed lower than the site now recommended by these and other authors. Even in this group, in which union between the head and the neck occurred in only about 25 per cent of the cases, the stability of the hip and the functional results were more satisfactory than those obtained by any of the various reconstruction operations.

For the entire series good or fair functional results were obtained in 80 per cent of the cases.

With the exclusive use of the high type of osteotomy the good results have been increased from 53 to 75 per cent; fair results have been reduced from 23 to 15 per cent, and poor results have been reduced from 23 to 10 per cent.

The authors consider that the ideal site for osteotomy is that corresponding to the level of the lower border of the femoral head, preferably passing through the trochanter just above the lesser trochanter. When union occurs after such osteotomies between the shaft and the head, between the head and the neck and between the shaft and the trochanteric fragment, the final result closely approximates the normal hip both anatomically and functionally.

In discussing the indications for osteotomy, the authors state that it will be necessary to study a large series of cases over at least a five year period before forming any positive conclusions. In general, however, present experience justifies the conclusion that osteotomy is preferable to reconstruction operations for the following reasons: 1. The operative technic is safer and simpler. 2. The mechanics of osteotomy more closely restore anatomic conditions for weight bearing in the hip. 3. Subsequent displacement and loss of support are less likely. 4. Function surpasses that of the best reconstructions and approximates that of osteosynthesis.

Osteotomy is contraindicated: (1) when the requirements are suitable for a bone graft or osteosynthesis; (2) if the fracture is of long duration and there is a small absorbed head with extreme lateral and upward displacement of the trochanter, where a reconstruction is preferable; (3) if an obviously necrotic head with osteoarthritis of an

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106. Speed, J. S., and Smith, H.: *Trochanteric Osteotomy for Ununited Fractures of Neck of Femur*, *South. M. J.* **34**:798-806 (Aug.) 1941.

excessive degree is present (aseptic necrosis of the head without arthritic changes is not considered a contraindication since material improvement in the nutrition of the head has frequently been observed following union with the shaft and the neck).

The operative technic recommended is similar to that described by McMurray except that sufficient exposure to divide the bone under direct vision is advised in order to insure a clear line of division with the proper inclination and without projecting or detached fragments.

The authors recommend a minimum period of cast immobilization of eight weeks and up to twelve weeks if union does not appear solid. In some cases displacement has occurred after only six weeks' immobilization. The general condition of the patient may necessarily terminate cast immobilization earlier than is desirable.

A position of slight flexion at the hip and the knee with a hinge joint in the cast at the knee reduces the joint stiffness.

The position of the osteotomy should be checked by roentgen examination through the cast at the end of three weeks, and if displacement has occurred, satisfactory reposition should be secured with the patient under general anesthesia, either by manipulation or further open operation.

[ED. NOTE: These reports constitute a valuable contribution to the problem of treatment of nonunion of the neck of the femur. Experience has shown that osteosynthesis is suitable for use in only a small percentage of the cases of nonunion. Reconstruction operations materially alter the normal anatomic weight-bearing conditions at the hip, and per se the percentage of good functional results leaves much to be desired. Whether the method of high trochanteric osteotomy reported in these articles will materially change the picture only time and the study of end results in a large number of cases can determine. Certainly the mechanics of the procedure are based on sounder principles than any of the reconstruction operations.]

*Delayed Unions, Malunions and Nonunions of Fractures of the Long Bones.*—Speed<sup>107</sup> classifies delayed unions of bone into (1) clinical, (2) roentgenologic and (3) functional.

Clinical delayed union is expressed by instability at the fracture plane, a tendency to develop a slowly progressive deformity or bowing and persistent swelling with edema and some localized pain at or near the fracture site. Continued pain and localized soreness in the fracture area after first mild attempts at active use always indicate delayed union and the necessity for further protective immobilization.

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<sup>107</sup> Speed, K.: Delayed Union of Bone, S. Clin. North America **21**:245-257 (Feb.) 1941.



Roentgenologic delayed union may be accompanied by all or none of the clinical findings. Roentgenologic delayed union is most often found in the peripheral bones, such as the carpus, the phalanges of the fingers or the toes and the scapula. The roentgen findings are demonstrated by a faint cloudiness of shadow between the fracture surfaces, which usually have lost their sharp edges, without excess callus. Calcification seems strikingly lacking; sclerosis of the fracture ends is lacking and, if it appears, may be accepted as definite evidence of nonunion.

Serial roentgenograms should be taken with exactly the same technic of exposure and interpreted by the same person, preferably the surgeon in charge who is familiar also with the clinical data.

Functional delayed union may be distinct from the other two types or combined with them. It is often betrayed by a complaint of weakness in the part, by delayed functional use and possibly by swelling and sensory and vascular changes of varying degree, mostly inexplicable on a clinical or a roentgenologic basis.

Some of these situations are explicable by factors under the control of the patient, e. g. psychic reaction, medicolegal controversies or malingering; others are to be explained on the basis of disturbed function, e. g. those due to age, cardiac action or endocrine and vitamin deficiencies.

The author discusses the various factors in the development of delayed union and their control. From the surgeon's standpoint, these include early adequate reduction of the fracture, the use of the proper type and length of immobilization, delay in active use of the extremity until callus formation is well advanced and a realization on the part of the surgeon that there is no short cut to bony union.

From the patient's standpoint, aside from such factors as age and condition of the vascular system (which are known factors), the more speculative considerations of physiologic and hematologic data, including blood chemistry, endocrine function and vitamin balance, must be taken into account.

It may be assumed that in a normal patient with adequate diet these factors are not material, but this should not prevent one from being on the alert to detect abnormalities of this type which might adversely influence the healing of fractures.

Milch<sup>108</sup> reports a case of delayed growth of the radius with relatively increased length and dorsal dislocation and painful instability of the ulna following an old fracture of the radius. The condition was corrected by cuff resection of the ulna, restoring the relative length of the two bones at the wrist. The ulnar prominence and instability and

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108. Milch, H.: Cuff Resection of Ulna for Malunited Colles' Fracture, *J. Bone & Joint Surg.* **23**:311-313 (April) 1941.

the painful dysfunction of the wrist were corrected. The same procedure is recommended for similar deformities following Colles' fractures in adults, although no reports of results are given.

Campbell and Boyd<sup>109</sup> report the use of vitallium screws as a method of fixation for onlay bone grafts in the treatment of ununited fractures. Campbell previously reported the end results of onlay bone grafts held by autogenous bone nails in 235 cases of nonunion; bony union was obtained in 93.6 per cent of the cases.

The present report includes an additional 60 cases in which vitallium screws were substituted for the autogenous nails as a means of fixation for the graft. End result study in this group shows bony union was obtained in 93.2 per cent, eventually the same as in the previous group.

The authors conclude: (1) that the use of vitallium screws rather than autogenous bone pegs for fixation of onlay grafts simplifies the operation; (2) that better mechanical fixation of the graft is afforded; (3) that bony union is obtained in practically an equal number of cases by the two methods, and (4) that the theoretic disadvantage of introducing a foreign body has little actual significance since vitallium is apparently inert in the tissues.

Stuck<sup>110</sup> advocates removal of tibial grafts of the massive onlay type with an osteotome in preference to a motor saw. He states that the grafts removed in this manner have the advantage of raw irregular edges and are not devitalized by overheating. These two features help in more rapid healing of the graft. He has used the method satisfactorily in 28 cases.

Meyerding and Cherry<sup>111</sup> report the technic and the end results in 15 cases in which some type of fibular stabilization or transplantation was performed for tibial defects. In 5 cases the loss of tibial continuity was due to hematogenous osteomyelitis; in 9 cases it was due to fractures, and in 1 it was due to pathologic fracture associated with osteomyelitis.

Various combinations of fusion of the upper or the lower end of the fibula to the tibia and fusion combined with transplantations of either the upper or the lower end or both ends of the fibula to the tibia were used according to the requirements of the bony defect present. In most of the cases there had previously been either primary osteo-

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109. Campbell, W. C., and Boyd, H. B.: Fixation of Onlay Bone Grafts by Means of Vitallium Screws in Treatment of Ununited Fractures, *Am. J. Surg.* **51**: 748-756 (March) 1941.

110. Stuck, W. G.: Preparation of Autogenous Bone Grafts with Osteotomes, *Am. J. Surg.* **51**:350-353 (Feb.) 1941.

111. Meyerding, H. W., and Cherry, J. H.: Tibial Defects with Nonunion Treated by Transference of Fibula and Tibiofibular Fusion, *Am. J. Surg.* **52**:397-404 (June) 1941.

myelitis or infection in connection with compound fractures. In 5 cases recurrent drainage occurred from preexisting osteomyelitis. In 3 cases in which fusion of the upper tibiofibular articulation was done, temporary peroneal palsy resulted.

In spite of such minor complications the final result in 15 cases was good, i. e. the patient had a limb which was satisfactory for weight bearing without support.

The various modifications and combinations described by the authors have wide applicability to tibial defects when for various reasons tibial grafting is contraindicated or needs reenforcing.

Wilson<sup>112</sup> gives a detailed description of a simple method of two stage transplantation of the fibula to the tibia for use in cases of complicated and congenital pseudarthrosis of the tibia.

The author states his belief that this method which fuses the upper and lower ends of the shaft of the fibula to the tibia is superior to the method of fusing the upper and lower tibiofibular articulations.

Wilson says that he believes the transference of the fibula into the tibia has a wide range of application and should be considered for all complicated or infected pseudarthroses, even if there is no great loss of tibial substance, particularly in cases in which tibial grafting appears of doubtful advisability.

The details of the operative technic, which is a two stage procedure, are accurately described.

Complete immobilization in a plaster cast is used for several months, and brace protection is maintained until the stability of the leg is assured.

The type of fibular transplantation described with the addition of bone grafts to the tibia in 5 cases was used in 4 pseudarthroses of the tibia following old compound fractures and in 5 congenital pseudarthroses. Union occurred in all the tibial pseudarthroses. Even in those cases in which additional tibial grafts were used the author feels that union was primarily due to the stability afforded by the fibular transplant. In 5 of the 9 cases spontaneous union of the tibia occurred as soon as the fibular transplant became fused to the tibia.

*Congenital Pseudarthrosis.*—Kite<sup>113</sup> reports the results in 15 cases of congenital pseudarthroses. He states that while cystic areas have been observed in many of the tibias before fracture occurs it is not a form of osteitis fibrosa cystica which is a general systemic disease while congenital pseudarthrosis is a local condition. Many patients show

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112. Wilson, P. D.: Simple Method of Two Stage Transplantation of Fibula for Use in Cases of Complicated and Congenital Pseudarthrosis of Tibia, *J. Bone & Joint Surg.* **23**:639-675 (July) 1941.

113. Kite, J. H.: Congenital Pseudarthrosis of Tibia and Fibula: Report of Fifteen Cases, *South. M. J.* **34**:1021-1032 (Oct.) 1941.

neurofibromas and café au lait spots which suggest a relation to von Recklinghausen's neurofibromatosis.

Owing to the high percentage of operative failures previously experienced most of the earlier writers on this subject advised delaying operation until the child was 6 to 8 years old. Kite disagrees with this because of the increase in permanent shortening and deformity of the leg if pseudarthrosis is permitted to persist for such a length of time. In the light of improvements in operative technic it appears that his contention is correct and that better functional extremities will result the earlier union in the tibia is secured.

In only 1 of Kite's cases was the fracture found at the time of delivery. In 8 of 15 cases the fracture developed during the first year and in 12 before the third year.

In all cases of this series the grafts used were autogenous; in most cases the "bone flap onlay graft" advised by Thornton was employed. In 11 of the 13 cases in which operation was performed bony union was eventually obtained, in some cases after two or more operations. The average shortening in 6 patients followed up to sixteen years was 10 cm.

Boyd<sup>114</sup> has developed and described a new principle in operative technic for congenital pseudarthrosis which apparently offers a much more certain method of attack on this difficult reconstructive problem. He uses a dual homogeneous graft which obviates many of the objections to the single graft and permits earlier operation in that the patient is not used as a source of the graft. Boyd also advises early operation to prevent deformity.

While a number of successful unions have been obtained by single massive grafts or by the multiple bone chip method described by Hallock, a study of the end results of such operations reveals definite criticisms. First, in a case of congenital pseudarthrosis the bone may be too soft to enable the threads in the vitallium screws to secure a firm grasp. Second, although a large amount of cancellous bone is packed about the fracture site, this bone is compressed by the organizing and contracting scar tissue which forms postoperatively about the fracture site. This results in a hemihourglass constriction at the site of union and a diminution in the size of the tibia at this point. This constriction predisposes to refracture and hinders the establishment of a marrow cavity through the former site of pseudarthrosis. This hemihourglass type of union also occurs in cases in which a defect in bone is bridged with an onlay graft and the defect is filled with cancellous bone. These factors are especially marked in cases in which the bone fragments are pointed at the ends. To overcome these objections it was decided to use the

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114. Boyd, H. B.: Congenital Pseudarthrosis: Treatment by Dual Bone Grafts, *J. Bone & Joint Surg.* **23**:497-515 (July) 1941.

dual bone graft. The advantages of this method are: 1. Better mechanical fixation is obtained. 2. The tibial grafts are revascularized slowly and provide rigid internal fixation over a long period. 3. The cancellous bone about the fracture is revascularized quickly and produces a strong osteogenic element. 4. With a single graft the screws may fail to hold in osteoporotic bone; with the dual graft a clamp is formed which compresses the tibial fragments between the two grafts. 5. The grafts form a trough to hold the cancellous bone which is packed around the fracture. 6. The grafts prevent compression of the cancellous bone by contracting fibrous tissue during the healing process. Hemihourglass constriction of the bone at the fracture site is minimized. 7. The diameter of the grafted bone is increased. 8. Partial absorption of one graft does not necessarily result in refracture and failure, since the second graft maintains internal fixation.

The operative technic is described in detail. It consists essentially in the use of two massive homogeneous onlay grafts placed across either side of the fracture site and spanning as much gap as necessary to maintain the full length of the leg. The grafts are held to the tibial fragments and to themselves by vitallium screws passing completely through the tibia and both grafts after the manner of a wood clamp. The space between the grafts and about the end of the fragments is filled in with cancellous bone.

The possible objection to homogeneous grafts is apparently answered by successful results in the 4 cases in which this method has been used as a corrective measure.<sup>115</sup>

[Ed. NOTE: It has been the privilege of one of us (J. S. S.) to follow these patients throughout the entire course of their treatment, and it appears from the results obtained that the technic described is a definite contribution to the treatment of congenital pseudarthrosis. Mechanically and physiologically the operation is based on sound principles. The attack is more direct, and the anatomic restoration of the tibia more nearly approaches the normal than that achieved with any of the other types of grafts or with such indirect methods as transplantation of the fibula. While the series is too small to permit forming a final judgment, the evidence so far is most encouraging. The use of the dual graft has been extended to the treatment of many other difficult types of non-union, particularly those in which there are small atrophic terminal fragments adjacent to joints or in which it is desirable to span a gap. The results have been most satisfactory.]

*(To Be Continued)*

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115. Boyd, H. B.: Personal communication to J. S. Speed, July 1942.

## INTRAPERITONEAL INJECTION OF VACCINE IN PREVENTION OF POSTOPERATIVE PERITONITIS

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The problem of peritonitis has long been puzzling and vexatious for the abdominal surgeon and the clinician as well. Some peritonitis probably occurs postoperatively in every case in which an abdominal operation is performed. Usually the degree of this peritonitis is slight, and the origin is chemical or traumatic. In intestinal operations, particularly on the large bowel, there is in most instances some bacterial peritonitis. Fortunately, if certain accepted principles are followed, in most cases the postoperative peritonitis is mild and nonfatal. However, when one is operating on malignant lesions of the large bowel, perforation of the growth and formation of abscess are often encountered. Occasionally, too, the anatomic situation of the malignant lesion places insuperable difficulties in the path of the surgeon.

It has been our hope that we might increase the resistance of each patient against fatal peritonitis and thereby reduce the number of postoperative deaths. We realized of course that in those cases in which there was a slow continuous leak of fecal material into the peritoneal cavity after operation we could probably accomplish little or nothing. Our hope was to save the patients who had, unavoidably, suffered some contamination at operation or in whose cases a slight intermittent leak of fecal contents developed postoperatively.

In 1928, Hermann, working in the Mayo Foundation, reported favorably on intraperitoneal injection of vaccine for the prevention of peritonitis produced experimentally in animals. In 1929, the vaccine was administered to patients. No ill effects resulted from the intraperitoneal use of vaccine, and the reactions following its use were never

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of sufficient severity to be alarming. In the ensuing years the vaccine has been given routinely to patients being prepared for surgical procedures of a major character on the intestine. Several statistical studies of the cases in which vaccine was given intraperitoneally have been made.

The preoperative rehabilitation of patients is an important factor in the prevention of postoperative peritonitis. It was soon realized that the administration of vaccine was only one of the preventive measures against peritonitis. When a number of papers appeared several years ago intimating that intraperitoneal vaccination was a minor or perhaps even useless protective measure in the preoperative program, we reviewed our clinical data and realized that these could be open to some objections, although the experimental data were much more definitely indicative of effectiveness.

With this in mind we again studied all the cases in which operation had been performed in the years 1932 to 1937, inclusive, and in which vaccine had been given intraperitoneally, and compared these cases with those in which vaccine had not been employed. There was a definite appreciable advantage in a lower mortality rate for the cases in which vaccine had been administered. There were, however, many factors involved, such as changes in preoperative preparation and operative technic during this period, that made the interpretation of the results confusing. The study brought to our attention the development of an elevated temperature after intraperitoneal vaccination, and our interest was attracted to correlate this with the postoperative death rate and particularly the death rate from peritonitis. The results of this examination will be given later in this paper. In view of the possible inconclusive results on the basis of examination of the accumulated series of operations, it was decided that the only method that would yield a definitive solution to our problem would be to institute an alternating controlled series of cases in which operation was performed. Therefore, with the assistance of the division of biometry and medical statistics, the work was planned and executed, and the results were analyzed.

In the experiments with animals previously referred to, several intraperitoneal injections of vaccines were given to immunize against peritonitis. In this series of observations on the value of intraperitoneal vaccination for human beings only one intraperitoneal injection was given. The results of these observations will be given in detail in the course of this study.

#### HISTORICAL

Wegener is credited with distinguishing between postoperative shock and peritonitis as early as 1877. He expressed the opinion that the absorption of toxic substances from the peritoneal cavity led to blood poisoning which really was the cause of death in cases of postoperative peritonitis.

Grawitz and Pawlowsky attempted to produce peritonitis experimentally by the intraperitoneal injection of bacteria. Many other workers have explored this field. The reader is referred to the theses of Hermann and Morton of the University of Minnesota Graduate School for a complete historical background of the experimental problem.

The problem of immunizing man and animals against peritonitis has been under investigation for a long time. Various methods of producing experimental peritonitis have been tried. Agents which would prevent the experimentally produced peritonitis were earnestly sought.

According to von Mikulicz, Issaeff found in 1894 that guinea pigs could be protected against otherwise lethal doses of *Vibrio comma* by the preliminary intraperitoneal injection of various agents, such as tuberculin, nucleic acid, normal human serum, broth, urine and physiologic solution of sodium chloride.

Miyake studied the problem in 1902 at the instigation of von Mikulicz. He was able to raise the resistance of guinea pigs to intraperitoneal injections of virulent *Escherichia coli* by the preliminary use of various substances, particularly a solution of yeast nucleins, the derived nucleic acid or a neutral sodium nucleinate. Whereas 1 cc. of physiologic solution of sodium chloride injected intraperitoneally doubled the resistance to virulent cultures of *Esch. coli* injected intraperitoneally, 1 cc. of 0.5 per cent solution of neutral sodium nucleinate multiplied the resistance twenty times. Furthermore, Miyake found that these injections were effective also against fecal soiling of the peritoneum.

Von Mikulicz attempted to apply these favorable experimental results to clinical practice. Intraperitoneal injections were given only three or four times because the unpleasant febrile reactions were severe. Von Mikulicz made his first preliminary report of the preoperative induction of hyperleukocytosis by subcutaneous injections of sodium nucleinate before the thirty-third congress of the German Surgical Association, meeting in Berlin in 1904.

Aschner and von Graff, working in von Eiselsberg's clinic, showed that with proper controls no prophylactic effect of the subcutaneous injection of sodium nucleinate against fecal soiling of the peritoneum could be demonstrated. However, the efficacy of intraperitoneal injections was established experimentally.

Hermann presented excellent experimental evidence in 1928 that in rabbits the repeated intraperitoneal inoculation of heat-killed mixed cultures of *Esch. coli* and green-producing streptococci causes a great increase of resistance to fatal peritonitis resulting from gross fecal soiling of the peritoneal cavity.

Morton reported in 1930 that rabbits could be protected against experimental peritonitis produced by virulent cultures of hemolytic



streptococci by preliminary intraperitoneal injection of 20 cc. of 20 per cent solution of dextrose. He found that several injections over a period of days gave better results than one injection or several injections given in one day. He found also that physiologic solution of sodium chloride injected intraperitoneally had value.

As a result of Hermann's experimental work, a vaccine was produced which has been used in our clinical practice in an attempt at intraperitoneal vaccination prior to operations on the colon. The method of preparing the vaccine and its mode of administration have varied little in the twelve years it has been given. During the first year or two in a number of cases two injections of vaccine were given before operation. This technic was abandoned later. In recent years one injection only has been employed routinely.

#### METHOD OF INTRAPERITONEAL VACCINATION

The patient reclines in bed on his back. The site at which the injection is given is of prime importance. If the lesion is on the left side of the abdomen, the injection should be on the right side. If the lesion is above the umbilicus, the point of injection should be below it. The injection should not be made more than 2 inches (5 cm.) from the umbilicus in any direction unless there is a special reason. The risk of perforation of the urinary bladder, the stomach, the liver, the cecum or the sigmoid is thus avoided. The midline is best avoided.

The skin is cleansed with alcohol and ether and painted with iodine or tincture of merthiolate. Drapes are placed over the operative field, and rubber gloves are worn.

A skin wheal is raised with procaine hydrochloride. The fascia and the muscle layers are infiltrated. A large caliber needle (no. 16 to no. 20) is used to puncture the abdominal wall through the area infiltrated with procaine hydrochloride. The point of the needle is introduced into the peritoneal cavity not more than  $\frac{1}{4}$  to  $\frac{1}{2}$  inch (0.6 to 1.3 cm.). The syringe is fastened to the needle, and gentle aspiration is effected. If any blood, gas or intestinal contents are aspirated, the needle is immediately withdrawn.

One cubic centimeter of the special vaccine diluted with 9 cc. of physiologic solution of sodium chloride is introduced through the needle into the peritoneal cavity by means of a 10 cc. syringe. The needle is withdrawn, and the patient is placed in Fowler's position for four hours. During this period the pulse rate, the blood pressure and the temperature are determined half hourly. After four hours, the patient is allowed up or permitted to lie down in bed. Codeine is given if necessary for cramps or pain. Epinephrine should be available in case of allergic or anaphylactic reaction.

For this series of observations, the vaccine was prepared as follows: A strain of *Esch. coli* and a strain of green-producing streptococcus obtained by culturing the peritoneal exudate of patients who had had fatal peritonitis were separately inoculated into bottles containing 150 cc. of 0.2 per cent dextrose broth. These bottles were incubated for twenty-four hours at 37.5 C.; at the end of this time they were centrifuged. The supernatant liquid was decanted, and 150 cc. of physiologic solution of sodium chloride was added to the centrifuged bacteria in each bottle. The bottles were then submerged in a water bath and kept at 70 C. for

one hour; at the end of this time the saline-suspended bacteria were mixed so as to have an equal quantity of *Esch. coli* and green-producing streptococci by volume. After we had cultured the mixture and were satisfied that it was sterile, 0.3 cc. of pure phenol was added to the mixture, and it was thoroughly shaken.

#### SUMMARY OF THE RESULTS OF THE TWO YEAR SERIES OF OBSERVATIONS

A review of our records of patients who had operations for lesions of the colon revealed that since the introduction of the use of intraperitoneal vaccination we have experienced a distinctly lower postoperative mortality rate than before. However, since in this period various changes in surgical technic and preoperative care had taken place which affected favorably the postoperative surgical mortality rate, it was considered that in order to have an absolutely dependable comparison of cases in which vaccine had been given with cases in which it had not been given, it would be necessary to set up a special investigation so as to maintain the same general operative conditions for both the group in which vaccine was given and the group in which it was not given.

In order to avoid all question as to the selection of cases for these groups, it was decided that the best method of obtaining a control series for the cases in which vaccine was given would be to make some arrangement which would completely avoid any element of personal judgment in the selection of cases. To accomplish this, it was arranged that patients who had conditions of the large intestine for which it had been decided to perform operation should be designated while they were in the medical hospitalization division as to whether they were or were not suitable candidates for the vaccine treatment. Patients who had extremely large lesions and for whom palliative operations alone were to be done, patients who had acute intestinal obstruction, patients who had ulcerative colitis and patients who had perforations and in whom active peritonitis was already present were considered unsuitable for administration of vaccine. The patients designated as suitable for vaccination were then arranged in order of registration number, and every alternate one was designated for administration of vaccine. Thus for every patient that received vaccine treatment there was to be an alternate one selected on exactly the same basis who was not to receive vaccine; a comparison of the mortality experience in the two groups, it was intended, would furnish controlled evidence as to whether the vaccine was helpful in affecting the mortality rate.

When, however, the study was actually put into operation, in some instances the administration or the nonadministration of the vaccine was determined by considerations not related to the study. Occasionally a patient who had heard about the vaccine previously would insist that he

have it, and occasionally the opposite was the case. Such patients were completely omitted from the observations at the outset. It had been intended that in instances in which a patient was to undergo more than one operation, as in the case of operations in two or more stages, if the patient had received vaccine in the first instance he should receive vaccine for all subsequent operations and if he had not received vaccine in the first operation he should not receive it in any subsequent operations. Had this been done, we should have had two clearcut groups: one group of patients who, whether they had had one or more operations, would have had the vaccine treatment in all of them and another control group of patients who whether they had had one or more operations, would not have had vaccine at all.

For the patients who had only one operation and for the first operation of those patients who had more than one, the arrangement of the study was fairly successful in having a patient treated with vaccine and the alternate one not treated. But when it came to the subsequent operations of those patients who had more than one, we were not able to exercise a strict dictatorial control in every instance. We were operating on human beings; we were dealing with factors that literally concerned life and death, and it is understandable that some of us who believed in the efficacy of vaccine should insist in certain instances that a patient receive vaccine in the second operation even though he had not received it in the first and that in some instances a patient who had received vaccine in the first operation might not receive it in the second because it was deemed unnecessary. These facts will explain why in the results to be presented the numbers of patients in the vaccinated and control groups are practically equal but why when we divide the series according to operations as such, putting all the operations prior to which vaccine was administered in one group and using as a control for this all the operations just prior to which no vaccine had been given, it will be found that more operations were performed without than with vaccine.

The period covered by this study was the two year interval May 1938 to April 1940, inclusive, and of the patients on whom operation was performed at the Mayo Clinic for lesions of the colon during this period, 480 were included in the analysis of this study. Of these 480 patients, 272 had only one operation, while the rest had operations in either two or more stages. The total number of operations, including the ones performed in multiple stages on the same patients, that were performed on those 480 patients was 639. Of the 639 operations, vaccine was administered prior to the surgical intervention in 258, and the remaining 381 operations were performed without the administration of vaccine beforehand.

The hospital mortality rates for the total group of these operations divided according to operative procedure are shown in table 1. It is seen, considering all the operations together, that after the 258 operations prior to which vaccine was administered there were 18 hospital deaths, yielding a hospital mortality rate of 7.0 per cent. After the 381 operations prior to which no vaccine was given there were 39 hospital deaths, yielding a mortality rate of 10.2 per cent. It is seen, then, that when one considers the over-all mortality rate for all operations, irrespective of whether these were in one or more stages and with these cases divided only according to whether vaccine was or was not administered prior to the operation concerned, the mortality rate is relatively almost half again as large in the group that did not have vaccine as in the group that did have it (10.2 as contrasted with 7.0 per cent).

TABLE 1.—*Comparison of Hospital Mortality Rates for Operations With and Without Intraperitoneal Vaccination in a Specially Conducted Study*

Operation	Vaccine Given			No Vaccine Given		
	Operations	Hospital Deaths		Operations	Hospital Deaths	
		Number	Per Cent		Number	Per Cent
Colostomy.....	107	2	2	142	5	4
Abdominoperineal resection.....	28	3	11	60	9	15
Posterior resection.....	21	3	14	34	5	15
Exteriorization operation.....	47	3	6	45	4	9
Ileocolostomy.....	21	1	5	26	2	8
Anterior resection.....	21	4	19	34	8	24
Resection of right portion of colon.....	13	2	15	40	6	15
Total.....	258	18	7.0	381	39	10.2
Peritonitis.....		10	3.9		25	6.6

The figures just quoted include all deaths occurring in the hospital after operation, regardless of cause of death. It is of some interest to consider only those deaths which were directly attributable to peritonitis or in which necropsy indicated the presence of peritonitis. This does not mean that these will include all the deaths in which peritoneal inflammation played some part, for naturally in cases in which there was no clinical evidence of peritonitis some peritonitis may still have been present, and even in deaths from causes other than peritonitis, such as pneumonia, peritoneal inflammation may have played a contributory role. However, of the 18 deaths of vaccinated patients, there were 10 in which peritonitis was indicated either clinically or pathologically, giving in relation to the 258 operations a death rate with peritonitis of 3.9 per cent. Similarly, of the 39 deaths occurring in the nonvaccinated group, there were 25 in which the presence of peritonitis was

indicated, yielding in relation to the 381 operations on the nonvaccinated group a death rate with peritonitis of 6.6 per cent. Thus we find, comparing only the deaths with peritonitis, that relatively more than half again as many deaths with peritonitis occurred in the group of nonvaccinated patients (6.6 as contrasted with 3.9 per cent). Even considering the deaths that could not be attributed from direct evidence to peritonitis, we find a slightly increased death rate in the nonvaccinated group. It is possible to attribute this either to failure to uncover evidence of existing peritonitis or to a possible contributory effect of peritoneal inflammation in deaths occurring primarily from other causes.

Still referring to the figures in table 1, if we consider separately the comparative rates for the different specific operations, we find that with each of the operations except posterior resection and resection of the right portion of the colon, the mortality rate for the vaccinated group is less than the comparable one for the nonvaccinated group. In the cases of posterior resection and resection of the right portion of the colon, the rates are practically identical. So far as these figures for the individual operations are concerned, it is to be realized that we are dealing with small numbers in each group and that because of this it would be hazardous to attempt to draw any conclusions regarding the relative efficacy of vaccine for different operations. We can judiciously conclude from these figures, however, that when all the operations are considered, the vaccinated patients have had an average better result of about 3 per cent as regards postoperative death rate.

We considered also the comparative results in the vaccinated and nonvaccinated series, with account taken of only one operation for each patient, i. e., an operation in a single stage or the first operation of a procedure in multiple stages. In the series in which no vaccine had been administered in the first operation there were 247 patients, and after the first operations in this series there occurred 18 hospital deaths, yielding a mortality rate of 7.3 per cent. In the series in which vaccine had been administered for the first operation there were 233 patients, and after the operations there were 13 hospital deaths, yielding a mortality rate of 5.6 per cent. When in this same series of first operations the deaths in which peritonitis was observed are considered, the hospital death rate in the nonvaccinated series was 3.6 per cent; in the vaccinated series, 2.2 per cent. We see, therefore, that when we consider only the first operation the same general comparative results are found. We also divided the entire series into several separate ones according to the operating surgeon, and for each surgeon separately, without any exception, the hospital mortality rate for the cases in which no vaccine had been used was relatively about half again as large as for those in which vaccine had been utilized.

We realize well that the difference in mortality rates experienced in this study between the nonvaccinated and the vaccinated series is not large and, particularly considering the number of factors involved, that the numbers in this study are not so large as desirable from a statistical viewpoint. However, the difference between the rates for the vaccinated and the nonvaccinated group taking into account the consistency of the separate subgroups is statistically significant; i. e., the probability of obtaining by chance as consistent a result in favor of the vaccine as shown in table 1 is less than 0.05.<sup>1</sup> We must emphasize again that we were dealing here with human beings as subjects and were using a treatment that offered possible protection against death; we consider that in accumulating even as large a series of alternate cases as we did, we have accomplished a rather difficultly achieved undertaking.

It might be said that difference in the mortality rates in the vaccinated and the nonvaccinated group was not large (3 per cent), but it must be realized that in dealing with rates as small as these, such a measure as vaccine inoculation cannot be expected to reduce the mortality rate a great deal in an absolute sense. Relatively, the reduction in rates is considerable, since it constitutes about a third of the death rate associated with nonvaccination. The consistency of the findings in this respect, whether we consider the entire group of operations as a whole or only the first operations in cases of multiple operations or the separate specific operations or the record of each surgeon separately, is impressive. Recalling the facts that these cases were divided into groups on a random basis and that there was absolutely no possibility of a selection of favorable cases for the vaccine treatment, such consistent results in favor of the vaccine cannot be attributed to chance. We conclude, therefore, that this study, which included 480 patients and 639 operations, definitely indicates that the administration of vaccine is of beneficial effect in decreasing the postoperative mortality rate.

#### STUDY OF POSTVACCINAL PEAK TEMPERATURE REACTIONS IN 1,990 PATIENTS

In the experience of the years 1932 to 1937, inclusive, there were performed 1,990 operations two or three days prior to which vaccine had been given intraperitoneally. An examination of the cases suggested a possible correlation between the degree of rise in the postvaccinal temperature and the postoperative mortality rate, especially the mortality

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1. Of the six operative groups of table 1 in which a difference of rates is shown in the results, all six were in the direction of favoring the vaccinated group. The probability of such a consistent series of differences occurring by chance is 0.016. The probability of a chance favorable difference as large as that found considering only the total average results is somewhat greater than 0.05.

rate associated with peritonitis. In table 2 is shown the hospital death rate associated with peritonitis for several groups divided according to whether in these cases the postvaccinal temperature peak was greater or not greater than 99.6 F., this temperature having suggested itself as a division point from perusal of the records. The hospital mortality rate associated with peritonitis for the cases in which the postvaccinal temperature rose no higher than 99.6 F. is only half that in the cases in which the temperature peak was greater than this value. There is a rise of mortality rate with the temperature of about 101.5 F., after which there is again some decrease but a relatively small one. The result in the group in which the peak temperature was less than 99.6 F. is striking. It suggests on its face that the absence of a marked increase of temperature after vaccination indicates that a relatively greater degree of

TABLE 2.—*Hospital Mortality Rate According to Postvaccinal Maximal Temperature*

Postvaccinal Maximal Temperature	Operations	Hospital Deaths with Peritonitis	
		Number	Per Cent
Less than 99.6 F.....	377	11	2.9
99.6 to 100.5 F.....	585	34	5.8
100.6 to 101.5 F.....	512	32	6.3
101.6 to 102.5 F.....	342	18	5.3
Greater than 102.5 F.....	174	9	5.2
Total.....	1,990	104	5.2

immunity is present. There is a sort of intraperitoneal Schick test phenomenon; i. e., those patients who do not react are relatively immune.

This finding can be rationalized on the idea that the reaction after vaccination with the dead organisms is a sort of abortive and localized peritonitis and that patients who are so constituted for one reason or another as to be relatively immune to postoperative peritonitis will be able to react to the vaccination and will therefore show less markedly the effect of localized peritonitis. The relative immunity of these patients may or may not have been produced by the vaccination itself. So far as the patients whose temperature rose to more than 99.6 F. are concerned, they too presumably possess a higher degree of immunity after vaccination than they would have had if vaccination had not been given. This is the conclusion to be drawn from our controlled study as well as from the comparison among the patients on whom operation was performed in the period 1932 to 1937 of the results for those who had had vaccination and those who had not. It should be realized that the postoperative death rate for the patients among these 1,990 in whom the peak temperatures had been more than 99.6 F. and for whom the mortality rate aver-

aged 5.8 per cent should not be compared with the postoperative mortality rate in the vaccine series of the control study, for operation was performed on these patients in a period in which the over-all postoperative mortality rate was considerably higher than in the years of our study.

So far as the immunity conferred on the patients who had a peak temperature greater than 99.6 F. is concerned, there is some reason to believe that the amount of conferred immunity is actually greater among those patients who have had a higher rise of temperature than among those who have had a lower. Clinical observation has given this impression, and the results in table 2 somewhat confirm this, since the patients who had a rise to more than 101.5 F. had a lower mortality rate than those who had a rise between 99.6 and 101.5 F. This apparently paradoxical result, that those who have a peak rise of about 1 F. from normal have a low mortality rate, while those who do have a rise to more than 100.5 F. have a lower mortality rate the higher the rise in temperature, is also not unreasonable if one looks on the low mortality rate in the first group as being the reflection mostly of an immunity already existing and only indicated by the low temperature, while the lower mortality rate among the rest of the patients who had vaccine as compared with those who did not have vaccine at all is a reflection of an immunity conferred by the vaccination itself.

If we adopt the premise that a patient having a postvaccinal temperature peak reaction of less than 99.6 F. is in a group relatively immune to peritonitis, then it follows that any measure which would result in a lowering of the postvaccinal temperature to a peak in the neighborhood of 99.6 F. would increase the relative immunity of the patient. If vaccination itself confers immunity, then those who in a second vaccination showed a lowering of temperature would be indicated as patients in whom the first vaccination had conferred a greater amount of immunity.

To examine this possibility, we had available records of 227 patients on whom operation had been performed in the years 1929 and 1930 and who had had two injections of vaccine. These were divided into three groups: those whose temperature peak was lower after the second injection than after the first; those whose peak was higher after the second than after the first, and those whose peak was not substantially changed (within  $\pm 0.2$  F.). The postoperative hospital mortality rates in this series are shown in table 3. It is seen that the lowest postoperative mortality rate was experienced in the group in which the second postvaccinal temperature was lowered from what it was after the first vaccination and that the highest was experienced in the group in which there was an increase, whereas the ones with substantially no change showed an intermediate mortality rate. Again it is to be noted that these mortality rates are not to be compared with those of our controlled



series, since the operations were performed in a period in which the level of mortality was higher and also because this is a special series in which extensive operations were performed. The comparison within this group, however, on the basis of temperature rise is valid, since the operations were all performed in the same period and the patients were a relatively uniform group in themselves.

### RESULTS AND CONCLUSIONS

An examination of data accumulated over a considerable number of years in which intraperitoneal injection of vaccine was used in connection with operations on the colon compared with cases in which no vaccine had been used showed a substantially smaller hospital mortality rate for the cases in which vaccine had been employed. However, these data consisted of the accumulation of the series of operations as they had been performed routinely at the Mayo Clinic. Since during the years in which these

TABLE 3.—*Comparison of Postoperative Mortality Rates According to Postvaccinal Rise of Temperature After Second Vaccination*

Postvaccinal Temperature	Operations	Hospital Deaths	
		Number	Per Cent
Lower after second vaccination.....	119	13	10.9
Higher after second vaccination.....	58	13	22.4
No significant change ( $\pm 0.2$ F.).....	50	6	12.0
Total.....	227	32	14.1

operations had been carried out there had been considerable change in the technic of preoperative care as well as in the technic of operations and postoperative care and since also in some years the proportion of cases in which vaccine had been used was larger than in other years, it was difficult to make a decisive judgment whether the decreased mortality rate could be attributed to the use of vaccine or to other measures and changed conditions.

For this reason a special study was set up which covered a period of two years in which the vaccine alternately was administered to a patient and was not administered to the next, the patients to whom vaccine had not been given being intended to serve as a control. From this controlled series were excluded at the outset any patients considered unacceptable for vaccine treatment, for example, patients with a large perforation. There were 480 patients included in the study on whom, counting operations in multiple stages, 639 operations were performed, 258 prior to which vaccine had been administered and 381 prior to which no vaccine had been administered. The postoperative hospital mortality rate in the group which was not vaccinated was 10.2 per cent, and in the group

which was vaccinated it was 7.0 per cent. If one considered only hospital deaths of patients in whom peritonitis had been found either clinically or at necropsy, the mortality rate from peritonitis for the 381 operations prior to which no vaccine had been administered was 6.6 per cent, and for the 258 operations prior to which vaccine had been employed it was 3.9 per cent. Thus the mortality rate in the group for which no vaccine had been administered was about half again as large as in the group for which vaccine had been used. Comparison was made separately according to type of operation and according to surgeon, and in all comparisons made there was a consistent advantage for the group which had received the vaccine in about the same proportion as indicated for the over-all average results. It was concluded that vaccine as administered intraperitoneally in the manner described in the text was of definite advantage in reducing postoperative hospital mortality rates following operations on the colon.

Certain of the statistics collected from previous results indicated that the postvaccinal rise of temperature is an indication of immunity to postoperative peritonitis. Among patients whose postvaccinal temperature did not rise higher than 99.6 F. there was a definite advantage in postoperative mortality rate over patients whose postvaccinal temperature exceeded 99.6 F. This indicated that a failure of temperature to exceed 99.6 F. after vaccination showed that the patient was relatively immune to postoperative peritonitis. The control study summarized in the preceding paragraph as well as the previously gathered statistics seems to show definitely that the vaccine produced an immunity in the cases in which the temperature did exceed 99.6 F.

It was thought that if the failure of the postvaccinal temperature to exceed 99.6 F. was an indication of a relatively great amount of immunity, in a series of cases in which two doses of vaccine had been given several days apart prior to operation, those cases in which the postvaccinal rise of temperature after the second administration was less than the postvaccinal rise of temperature after the first administration would be presumably those in which a greater amount of immunity had been conferred by the first vaccination. If so, the postoperative mortality rate in this group should be less than in a group in which the patients had received two administrations of vaccine but in which the temperature after the second administration was higher than that in the first. This would indicate the active function of the first vaccination in conferring immunity as well as corroborate the idea that the postvaccinal rise of temperature gave an indication of the degree of immunity conferred. A series of such cases in which two vaccinations had been administered was available from previously accumulated data, and an examination of this showed that the postoperative mortality rate in the group in which the rise of temperature after the second vaccination was lower than after

the first was considerably lower than the postoperative mortality rate in the group in which the postvaccinal rise of temperature after the second was higher than that after the first.

The results just summarized suggest that the efficiency of intraperitoneal injection of vaccine in conferring immunity could be increased if instead of a single administration prior to operation more than one vaccination were utilized and that this procedure could be guided by the postvaccinal rise of temperature after the first vaccination. A plan that might be suggested is to include multiple intraperitoneal injections over a period of six to eight days prior to operation.

In these studies an intraperitoneal vaccine consisting of a sterile suspension of *Esch. coli* and green-producing streptococci was utilized. Other studies, including that of Morton, who accumulated data following intraperitoneal injection of solutions of sodium chloride, indicate that other solutions injected intraperitoneally may also be effective against postoperative peritonitis. In any further controlled studies of this subject, it is therefore to be kept in mind that other solutions than the ones we utilized might also be included.

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## RESULTS FOLLOWING LIGATION OF THE INTERNAL CAROTID ARTERY

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It has long been known that ligation of the internal or common carotid artery is followed by (1) a high mortality rate and (2) a high percentage of cerebral complications. Some of the patients in whom cerebral complications develop survive with residual sequelae, such as varying degrees of hemiplegia, aphasia, mental changes and epilepsy. In prelisterial days the surgical mortality rate from carotid ligation approached and frequently surpassed 50 per cent. It has since been learned that the mortality rate is less when wounds are clean and that sepsis was responsible for many deaths through the intravascular spread of an infected thrombus into the cranial chamber. However, precisely the same sequence of events occurs with and without sepsis; the only difference is in the relative frequency. There are two causes of death and disability: (1) cerebral anemia from inadequate collateral circulation through the circle of Willis, the effects of which appear immediately and may be abrupt or progressive, and (2) cerebral thrombosis and embolism, the effects of which are late in appearing, i. e., develop twelve hours to several days later, and are usually abrupt, though at times a preceding small attack may warn of the impending event.

The purpose of this communication is to show that (1) by care in the preoperative tests for the adequacy of collateral circulation in the brain and (2) by the proper choice of the methods of ligation these risks can now be largely eliminated.

Pilz<sup>1</sup> collected 600 cases of common carotid ligation, the mortality rate being 38.5 per cent and cerebral complications being present in 32 per cent. Lefort<sup>2</sup> reported a mortality rate of 54.5 per cent. Wyeth<sup>3</sup> and Ballance and Edmunds<sup>4</sup> reported 789 collected cases in each of

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1. Pilz, C.: Zur Ligatur der Arteria carotis communis, nebst einer Statistik dieser Operation, *Arch. f. klin. Chir.* 9:257, 1868.

2. Lefort: A. carotis, in Archambault; Arnould, J.; Axenfeld; Baillarger, and others: *Dictionnaire encyclopédique des sciences médicales*, Paris, 1879, vol. 12, p. 621.

3. Wyeth, J. A.: *Essays on the Surgery and Surgical Anatomy of the Great Vessels of the Neck*, New York, William Wood & Company, 1879.

4. Ballance, C. A., and Edmunds, W.: *A Treatise on the Ligation of the Great Arteries in Continuity*, London, Macmillan & Co., 1891.

their writings with a mortality rate of 41 per cent (they probably had reference to the same material). The writings of these authors give a fair estimate of the risks to life in the days when operations were almost always attended by sepsis.

In 1891 Zimmermann<sup>5</sup> collected 65 cases reported since 1880 with a mortality rate of 31 per cent and an incidence of cerebral complications of 26 per cent, and in 1899 Siegrist<sup>6</sup> reported 825 cases collected since 1880 with a mortality rate of 40 per cent. More recently, Cauchoix<sup>7</sup> reported 150 cases of ligation of the common carotid with a mortality rate of 10 per cent and 13 cases of ligation of the internal carotid with a mortality rate of 16.7 per cent; Walcker<sup>8</sup> reported a mortality rate of 40 per cent in 601 collected cases; Matas,<sup>9</sup> in 66 cases of his own (60 cases of ligation of the common carotid and 6 of ligation of the internal carotid), had 8 deaths (including 2 reported as due to angina)—representing a death rate of 12 per cent. The report of Matas brought the risk to the lowest figure yet obtained and represented the best work of an individual investigator rather than an ensemble of results collected from the literature. I have made no effort to separate ligations of the internal and common carotid arteries. It is frequently stated that ligations of the common carotid are less dangerous than those of the internal carotid because of the collateral circulation through the external carotid in the former. Theoretically this appears reasonable, and perhaps there may be a slight difference, but I doubt that it is much. A recent report by Watson and Silverstone<sup>10</sup> of a death rate of 55 per cent and of an incidence of cerebral complications of 70 per cent in their 20 cases should be noted in passing. In all of their cases, however, the ligations were done in conjunction with the removal of large carcinomatous masses (many of them ulcerated and infected) in the neck. Such statistics cannot give a fair appraisal of the risks incurred with simple ligations of the carotid arteries, but they do indicate the dangers that attend the procedures.

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5. Zimmermann, W.: Ueber die Gehirnerweichung nach Unterbindung der Carotis communis, Beitr. z. klin. Chir. 8:364, 1891.

6. Siegrist, A.: Die Gefahren der Ligatur der grossen Halsschlagadern für das Auge und das Leben des Menschen, Arch. f. Ophth. 1:511, 1900.

7. Cauchoix, cited by Niedner, F.: Ueber die Unterbindung der Arteria carotis, Beitr. z. klin. Chir. 171:524, 1941.

8. Walcker, F.: Einige neue Wege zur Vorbestimmung der möglichen Komplikationen nach der Unterbindung der A. carotis communis, Arch. f. klin. Chir. 130:736, 1924.

9. Matas, R.: Classified Summary of Six Hundred and Twenty Operations upon the Blood Vessels, Performed for All Causes, Tr. Am. S. A. 58:335, 1940.

10. Watson, W. L., and Silverstone, S. M.: Ligature of the Common Carotid Artery in Cancer of the Head and Neck, Ann. Surg. 109:1, 1939.

RESULTS IN THIS SERIES OF EIGHTY-EIGHT LIGATIONS  
(PARTIAL AND TOTAL)

In this series, except for 3 ligations of the common carotid, all have been ligations of the internal carotid. In each of the 3 exceptions, however, in addition to the common carotid the external carotid was tied, so that the equivalent of ligation of the internal carotid was done. All ligations were performed by myself or my associates, and all were "clean cases." In all but 3 of the cases of partial ligation, total ligation was done subsequently. In the overwhelming percentage of the cases the ligations were performed for verified arterial or arteriovenous aneurysm of the brain; in a few they were done for brain tumor. The ligations may be divided into three groups: (1) partial ligation in the neck (with fascial bands), 25 cases; (2) total ligation in the neck, 36 cases; (3) total intracranial ligation (with silver clips), 27 cases. The total number of cases was 88.

*Partial Ligation in the Neck.*—Partial occlusion of the internal carotid with fascial bands was done in 25 cases. Immediate cerebral complications developed in 3 cases (12 per cent); death occurred in 1 case (4 per cent).

The single death was due to an aneurysm that was known to have ruptured at the time of the ligation. The ruptured aneurysm therefore probably did not contribute to the death but perhaps did induce the paralysis.

In the 3 cases in which there were immediate complications, the band was removed in each instance within a few hours with the following results: complete return of function in 1; complete return of speech but not of motor power in 1; no improvement in 1.

In 15 cases the lesion for which the carotid was ligated was intracranial arterial aneurysm; in 9 cases it was intracranial arteriovenous aneurysm.

The ages of the patients were 33, 36, 36, 38, 38, 40, 45, 45, 48, 50, 51, 52, 53, 54, 56, 58, 60, 61, 67, 68, 68, 68, 70, 72 and 73 years.

The ages of the 3 patients with cerebral complications were 56, 58 and 70 years respectively.

*Total Ligation in the Neck.*—Total ligation in the neck was done in 36 cases. In 7 cases it was done after partial ligation in the neck; in these 7 cases there were no immediate or late cerebral complications, and there was 1 death. In 12 cases it was done after intracranial clipping of the carotid; in these cases there were no cerebral complications or deaths. In 17 cases it was done without any prior attack on the artery; in these cases there were no immediate cerebral complications, but in 1 case there were late cerebral complications followed by death.

The age of the patient with the cerebral complication (hemiplegia) was 13 years. Hemiplegia occurred suddenly twenty-four hours after

the artery had been tied. The patient died eighteen days later. Post-mortem examination was not obtained. This complication and death could, I am sure, now be avoided by tying the artery over a band of fascia lata.

The death noted as following partial ligation, which was done when the patient was dying and was not in any way responsible for her death, was shown at necropsy to have been due to multiple scattered venous thrombi. In view of these observations the ligation was ill advised. Her original lesion was a carotid arteriovenous aneurysm. It was for this that the original partial ligation had been performed. The relation, if any, between this lesion and the multiple venous intracranial thrombi is not clear.

The ages of the patients in whom the internal carotid was ligated were as follows: (1) of those whose internal carotid was ligated after partial occlusion—38, 48, 50, 52, 53, 54 and 68 years; (2) of those whose internal carotid was ligated after intracranial clipping—20, 20, 23, 28, 36, 37, 38, 42, 43, 47, 48 and 54 years; (3) of those whose internal carotid was ligated without prior attack on the artery—13, 18, 23, 23, 24, 27, 28, 32, 35, 36, 39, 43, 45, 47, 48, 48 and 55 years.

In 15 cases the lesion for which the carotid was ligated was intracranial arterial aneurysm; in 20 cases it was carotid-cavernous and cerebral arteriovenous aneurysm; in 1 case it was tumor of the gasserian ganglion.

*Total Intracranial Ligation.*—The internal carotid was clipped intracranially in 27 cases. In 6 cases this was done after partial ligation in the neck; in these cases there were no cerebral disturbances, but there was 1 death. In 6 cases the clipping was done after total ligation in the neck; in these cases there were no cerebral disturbances or deaths. In 15 cases the clipping was done without prior attack on the artery in the neck; in 1 of these cases there was an immediate cerebral complication.

The single death (giving a mortality rate of 4 per cent) was due to rupture of the carotid when an undersized clip was applied to a greatly enlarged arteriosclerotic artery. The single immediate cerebral complication (hemiplegia) was due to inadequate collateral circulation in the circle of Willis. Since this was known beforehand from the positive reaction to the Matas test, it was poor judgment to take the chance involved in clipping the artery intracranially.

In 16 cases the lesion for which the internal carotid was clipped intracranially was intracranial arterial aneurysm; in 9 it was carotid cavernous arteriovenous aneurysm; in 2 it was tumor of the gasserian ganglion.

The ages of the patients were 18, 20, 20, 21, 23, 23, 23, 24, 27, 28, 32, 36, 38, 37, 42, 43, 45, 45, 45, 47, 48, 52, 53, 53, 54, 58 and 60 years.

*Summary of Results of All Eighty-Eight Ligations.*—Among all 88 cases in which ligation was done there were immediate cerebral complications in 4, or 4.5 per cent, late cerebral complications in 1, or 1.1 per cent, and deaths in 4, or 4.5 per cent.

#### COMMENT

It is certain that in 1 case of total ligation the death was in no way connected with the operation, for the patient was dying at the time ligation was done. The operation was a desperate but ill considered attempt to do something for a condition which could not be diagnosed but which was thought to be related to an arteriovenous aneurysm which had nothing to do with the patient's impending death. In another case death was due to rupture of an intracranial aneurysm which was known to have broken at the time the operation was performed. If these 2 cases are eliminated, the mortality rate is 2.25 per cent. With greater care in applying an intracranial silver clip another death would have been prevented, and finally, if a band of fascia had been interposed between the internal carotid and the silk ligature, there is reason to believe that the late-appearing hemiplegia and subsequent death would have been avoided. With careful preoperative care in the choice of ligations of the internal carotid and with the best of operative skill, ligations of this vessel should now be possible with little risk.

From the complications already mentioned it can be seen that partial ligations are the most hazardous. There can be no doubt that the application of the Matas test<sup>11</sup> used throughout this series, i. e. compression of the internal carotid with the finger for ten minutes to determine whether or not cerebral functions are disturbed, is responsible for the low figures both of mortality and cerebral complications. Without this test and the resulting operative attack, the results in this series would scarcely have been different from those of other reports. A high percentage of patients, regardless of age (but certainly increasing with age), will not tolerate total ligation of the carotid, but by partial closure of the carotid the cerebral collateral circulation becomes quickly established, and complete closure can be safely concluded later. The exact time between the partial and total closures of this vessel has been determined empirically. At first an interval of four to six weeks was thought to be advisable, but gradually this was lessened until now a week is considered ample, and in one of the most severe tests in this series (a large carotid aneurysm) the total closure was made after four days. By this means

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11. Matas, R.: Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries, J. A. M. A. 63:1441 (Oct. 24) 1914.



the reduced flow of blood through the internal carotid is adequate for the cerebral blood supply, but at the same time the demand is made for the anterior and posterior communicating arteries to supply the deficit that is created.

In none of the cases was there any disturbance when total ligation followed preliminary partial closure. And without the Matas test most if not all of these patients would certainly have been lost or badly crippled by the effects of inadequate cerebral circulation if the total occlusion had been done first.

Only once did preliminary partial ligation fail to establish the collateral circulation so that total occlusion could be performed. This was in the last case included in this report. Two months earlier I had done partial ligation of the carotid for post-traumatic carotid-cavernous arteriovenous aneurysm. The patient was so much improved that he was allowed to return home with the hope that the intra-arterial thrombosis would clear the lesion in time. When he subsequently returned, compression of the carotid could still not be sustained, numbness of the arm developing within a minute. The lumen of the carotid was then further reduced by another band. At the time of the operation (with the patient under local anesthesia) temporary direct occlusion of the artery with forceps produced precisely the same numbness of the arm as the Matas test. It can only be assumed that the circle of Willis was congenitally defective (the patient's age at the time of writing is 36), that probably one of the communicating branches was absent and that the other was too small to maintain the cerebral circulation. One week later the artery was totally ligated in the neck and clipped intracranially without any untoward effects.

#### PARTIAL CLOSURE OF THE INTERNAL CAROTID

Throughout this series of cases a band of fascia lata was used for partial closure of the internal carotid. It has the advantage of a living tissue, is soft and can therefore be removed with ease and safety if signs of vascular anemia develop. Dr. W. S. Halsted<sup>12</sup> performed many experiments on animals, using all types of bands, and concluded that metallic (aluminum) rolled bands were superior, even though at times the vessel was eroded by the band. His objection to fascia lata was the disintegration of the fascia due to the strong arterial pulsation. However, his experiments were performed on the abdominal aorta, which is larger and has a more violent pulsation. Even on the internal carotid the fascia does disintegrate, the fibers fragmenting, but apparently this

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12. Halsted, W. S.: Partial, Progressive and Complete Occlusion of the Aorta and Other Large Arteries in the Dog by Means of the Metal Band, *J. Exper. Med.* **15**:373, 1909.

can be entirely overcome either by doubling the fascial band or encircling the vessel twice; the fascia then does not break up. In 4 instances I have subsequently removed the section of the carotid covered by the double bands and subjected them to microscopic study; the fibers appeared to be intact after intervals of two to four months. One noticeable difference appears to be evident, that there is always a reaction and deposition of new tissue about a band, but it is far greater when the band is single and the fibers fragmented; the fibers are then engulfed in such a dense, bulbous, fibrous mass that the original fascia (after two months) can scarcely be found on gross dissection. When the band is double, the original band is just as distinct as when it was applied. With either the single or the double layer of fascia, however, the result is essentially the same. In addition to the constriction by the band itself, there is gradually added an increasing constriction of the lumen by the added connective tissues. In time total occlusion would probably ensue.

The first application of fascial bands to human arteries was probably made by Perthes<sup>13</sup> and has since been used by Freeman<sup>14</sup> and in improved fashion by Kerr.<sup>15</sup> Pearse<sup>16</sup> recently suggested cellophane bands because of the marked connective tissue reaction that follows and which in time gradually obliterates the lumen, but I see no advantage over the fascial bands which do precisely the same thing though perhaps more slowly. There is apparently no need for greater rapidity of progressive constriction of the lumen than that produced by fascia lata. Whether or not the lumen would be too rapidly constricted by the cellophane reaction I do not know.

The degree of initial constriction of the lumen of the carotid is all important and requires great care. At best it is a rough estimate guided by the appearance of the constricted region and by the effect on the pulsation above the band. Since in 3 of my earlier cases cerebral disturbances developed owing to too much constriction, I have preferred to err on the side of too little constriction rather than that of too much and to depend on the subsequent tissue reaction to increase it. Roughly a reduction of the lumen by one half is safe and has led to no cerebral symptoms in recent years. This still leaves a good pulse above but one distinctly less than that below the band. It is less than the thrill stage,

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13. Perthes: Ueber die Ursache der Hirnstörungen nach Karotisunterbindung und über Arterienunterbindung ohne Schädigung der Intima, *Arch. f. klin. Chir.* **114**:403, 1920.

14. Freeman, L.: The Causation and Avoidance of Cerebral Complications in Ligation of the Common Carotid Artery, *Ann. Surg.* **74**:316, 1921.

15. Kerr, H. H.: Fractional Ligation of the Common Carotid Artery in the Treatment of Pulsating Exophthalmos, *Surg., Gynec. & Obst.* **46**:565, 1925.

16. Pearse, H. E.: Experimental Studies on the Gradual Occlusion of Large Arteries, *Tr. Am. S. A.* **58**:443, 1940.

which is much too far. In none of the partial constrictions that have been done in the past four years have there been any adverse after-effects.

In 1 of the earlier cases removal of the fascial band restored the cerebral functions. Similar results have been reported by Matas (aluminum band) and Moses (fascial band).<sup>17</sup> In order to appraise the immediate response to partial ligation, the operation should be performed with the patient under local anesthesia, or at least one of the anesthetics from which consciousness is quickly restored should be used. It is important also that the band be removed when the first sign of cerebral failure is manifest, for progression of the disturbance is probable.

#### CAUSE OF LATE CEREBRAL DISTURBANCE FROM CAROTID LIGATIONS

The immediate cerebral complications, of which hemiplegia is the outspoken evidence, are clearly explained on the basis of inadequate circulation to the affected side of the brain. The late cerebral involvement is just as certainly explained on the basis of a propagating thrombus in the carotid, or possibly in some cases an embolus that has broken off from a thrombus and lodged in the cerebral arteries. Usually the onset is precipitate, but there may be premonitory cerebral attacks with recovery, followed in the succeeding twenty-four to forty-eight hours by the complete loss of function.

The pathologic reports confirming this view are not numerous but are conclusive. Zimmermann<sup>5</sup> collected 5 reported cases with post-mortem examinations of the carotid artery following ligations; in all there were thrombi extending the length of the carotid in the neck. Two of the specimens were examined intracranially, and all three branches of the carotid (in the brain) were filled with a continuation of the thrombus (Verneuil's case, 1871) and (Schänborn's case, 1879). In 4 of his own cases the entire carotid in the neck was closed by a thrombus, and in 1 of these it was continuous into the ophthalmic and middle cerebral arteries. Stierlin and Meyerburg<sup>18</sup> reported a specimen obtained after a bullet wound in the neck in which the internal carotid was not torn; the thrombus extended from a point 4 or 5 cm. above the carotid bifurcation into the anterior cerebral and middle cerebral arteries and their branches. In another of Zimmermann's cases (following thyroidectomy), the thrombus extended down the external carotid into

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17. Moses, H.: *Hirnstörungen nach Carotisunterbindung*, Zentralbl. f. Chir. 9:321, 1921.

18. Stierlin and Meyerberg: *Die fortschreitende Thrombose und Embolie im Gebiet der Carotis interna nach Contusion und Unterbindung*, Deutsche Ztschr. f. Chir. 142:1, 1920.

and up the internal carotid artery and closed the middle cerebral artery. Cerebral symptoms appeared suddenly four days after the operation, and death occurred two days later. Perthes traced a postoperative thrombus (artery tied at the base of the skull) into all three intracranial branches of the internal carotid. Paralysis and aphasia appeared eight hours after the ligation and were complete in three hours. Death occurred six days later. The intima and the media had been cut by the ligation. In another of Perthes' cases hemiplegia developed during the night following ligation of the carotid. There were a thrombus at the site of the ligature and an embolus in the terminus of the intracranial portion of the carotid. Apparently the thrombus was not continuous, but a fragment of it was carried up the carotid.

An interesting case was recorded by Esmarch.<sup>19</sup> While an aneurysm of the carotid in the neck was being palpated, the patient suddenly became hemiplegic and died three days later. Necropsy showed a thrombus formation (from an embolus) in the internal carotid from the ophthalmic artery into the middle cerebral and anterior cerebral arteries and their branches.

In a personal communication Dr. Cyril Courville, of Los Angeles, has forwarded me unpublished reports of carefully studied postmortem examinations made in 2 cases. In 1 case a thrombus extended the entire length of the internal carotid and into the anterior and middle cerebral arteries. In the other the artery in the neck contained a thrombus that extended part way up the neck, and an embolus had lodged in the middle cerebral artery, the anterior cerebral artery being intact.

I<sup>20</sup> recently reported a necropsy specimen (nontraumatic and non-operative) from a spontaneously arising thrombus that extended continuously from the bifurcation of the carotid into the middle cerebral artery and its branches and for some distance into the anterior cerebral artery. It apparently arose from a defective calcified area in the artery within the carotid canal (see illustration).

Pettermann<sup>21</sup> reported 4 cases of sudden cerebral death after carotid ligations with postmortem studies in 3. Softening in the brain was reported in one, and a thrombus of the internal carotid extending from the ligature was reported in another. Although he explained the cerebral disturbances by propagation of thrombi (and they undoubtedly

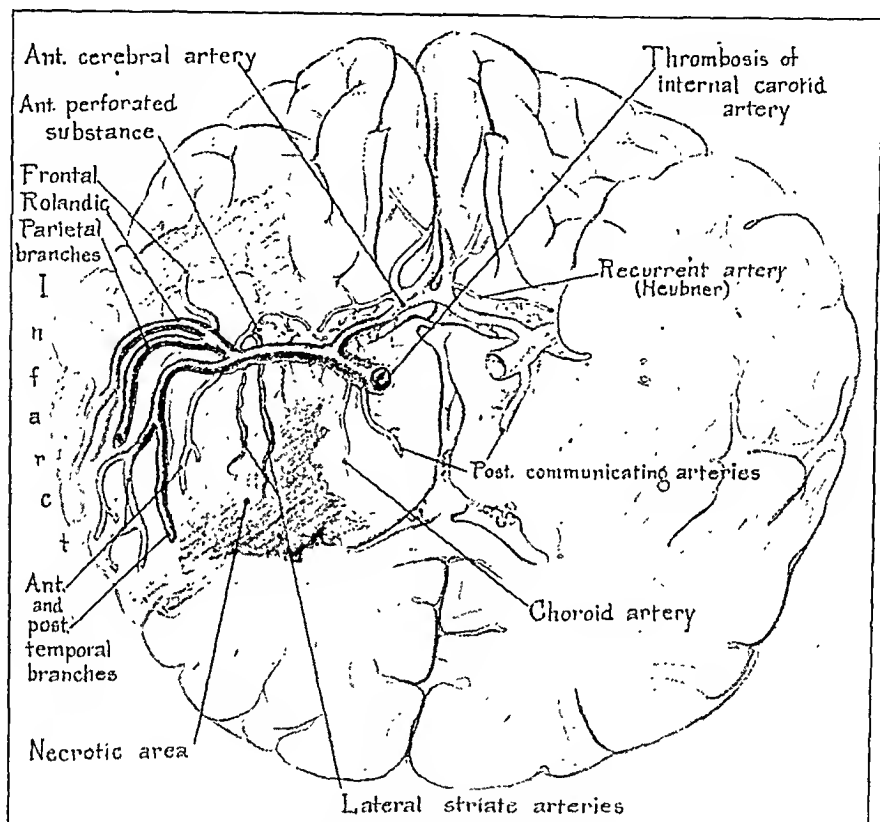
19. Esmarch, F.: Embolische Apoplexia durch Lösung von Fibringerinnseln aus einen Aneurysma der Carotis, *Virchows Arch. f. path. Anat.* **11**:410, 1857.

20. Dandy, W. E.: Carotid-Cavernous Aneurysms (Pulsating Exophthalmos), *Zentralbl. f. Neurochir.* **2**:77, 1937.

21. Pettermann: Unterbindung der A. carotis interna, *Zentralbl. f. Chir.* **59**: 3073, 1932.

are due to this), the pathologic studies were not sufficiently complete to use for evidence.

Fetterman and Pritchard<sup>22</sup> reported the postmortem observations in the case of a patient aged 37 whose internal carotid had been ligated one and one-half years earlier; two and one-half hours after the operation aphasia and right hemiplegia resulted. The internal carotid (intracranially) was completely obliterated. No note was made con-



Drawing of a thrombus extending from the common carotid artery through the entire length of the internal carotid artery and into the three intracranial branches of this vessel. The cause of this thrombus is not known, but the oldest part of the thrombus appears to be in the cavernous portion of the internal carotid, and here alone there is marked calcification in the media, principally in the elastic layer and the thinning portion of the intima.

cerning the extension of the thrombus into the middle cerebral artery, nor can one determine this from the excellent photographs of the exterior of the cerebral vascular tree. The posterior communicating

22. Fetterman, J. L., and Pritchard, W. H.: Cerebral Complications Following Ligation of the Carotid Artery, *J. A. M. A.* **112**:1317 (April 8) 1939.

artery was absent on that side and small on the other, but the anterior cerebral artery appears to have been of ample size to take care of the collateral circulation.

In a recent communication Schorstein<sup>23</sup> argued at some length to refute this explanation of the cause of cerebral complications after carotid ligations. These he explained by anoxemia and without actual occlusion of the vessels. He based his conclusions on 3 cases reported by others, in none of which was a thrombus seen at autopsy. However, a lesion of this kind may well have been missed. He admitted that in 1 of the cases the local pressure of the intracranial aneurysm may have been responsible; this compression would, of course, act precisely like an intravascular occlusion from a thrombus, and the end result would therefore be essentially the same.

Schorstein failed to differentiate between the immediate and late sequelae of carotid ligations. The former, occurring within the first six or eight hours, are unquestionably due to anoxemia, but after this period, in which the cerebral circulation has been tested and proved adequate, subsequent disturbances of the brain can be due only to intracranial occlusions from thrombi or emboli.

#### PREVENTION OF THROMBI AND EMBOLI IN CLEAN WOUNDS

From a long and carefully studied series of vascular occlusions, Dr. Halsted<sup>24</sup> concluded that injury to the intima was responsible for the development of intravascular thrombi. This view has since been amply supported by experimental and clinical data. A silk ligature applied tightly enough to obliterate a large artery always cuts the intima and the media, and this wound is the starting point for the thrombus. Doubtless the diminished pressure and flow within an occluded large artery is also an important item in thrombus formation. This was long ago stressed by Virchow and later by Senn<sup>25</sup> and by Perthes. A retarded circulation is doubtless also an important factor in the formation of venous thrombi and subsequent pulmonary emboli.

Realizing the importance of intimal injury from ligatures as the cause of late cerebral complication, Perthes suggested two methods of obliterating the artery by which the intima would not be injured: (1) by tying the artery with a band of fascia lata (using a knot) and (2) by tying the artery around an interposed bar of fascia lying on one side

23. Schorstein, J.: Carotid Ligation in Saccular Intracranial Aneurysms, *Brit. J. Surg.* 28:50, 1940.

24. Halsted, W. S.: *The Effect on the Walls of Blood Vessels of Partially and Completely Occluding Bands*, Baltimore, Johns Hopkins Press, 1924, p. 585.

25. Senn, N.: *Cicatrization of Blood-Vessels After Ligature*, *Tr. Am. S. A.* 2:249, 1885.

of the artery. Kerr improved this procedure by suturing the fascia (for partial occlusion). In recent cases I have placed a band of fascia around the carotid for either partial or complete occlusions; in the former the artery is subsequently tied with silk around the band of fascia, and in the latter the silk ligature is applied over the fascia to make the total ligation initially. I feel certain that had this been done in my single case of late cerebral complication and death, the disaster would not have occurred.

#### CLIPPING THE CAROTID INTRACRANIALY

Clipping the carotid intracranially has become a frequently used procedure in the treatment of certain intracranial aneurysms, both arterial and arteriovenous, and is occasionally necessary with tumors in the region of the cavernous sinus and the gasserian ganglion. The clip is placed astraddle the artery and closed by light compression. Except for a death from rupture of an oversized arteriosclerotic artery when applying an undersized clip there were no fatalities. The only cerebral complication was an immediate one which occurred when the artery was closed despite a preoperative warning by the Matas test that the collateral circulation was inadequate (pressure on the carotid was tolerated only five minutes). Such developments as these would now be better handled and the sequelae avoided. I have had occasion to reexpose at operation two clips, each after a period of several months, and in neither of the cases was there any thrombus formation on the cardiac side of the clip, the carotid being normally full and compressible about the clip. And in no case was there any late cerebral complications. It therefore appears to be an ideal method of occluding the internal carotid intracranially. And because the intracranial division of the internal carotid is so much smaller than the cervical portion (perhaps five times as small), I feel more secure against thrombus formation when it is clipped intracranially than when the artery is ligated in the neck. When both intracranial and cervical ligations are indicated, I therefore prefer to do the intracranial one first. Certainly the possibility of a propagating thrombus is less with a small artery than with a large one.

#### SUMMARY AND CONCLUSIONS

Eighty-eight partial and total ligations of the internal carotid artery are included in this report. Death occurred in 4 cases (a mortality rate of 4.5 per cent); immediate cerebral complications were present in 1 case (1.1 per cent), and late complications were present in 4 cases (4.5 per cent). By evaluating and avoiding the causes and the sequelae the subsequent results should be improved.

The Matas test, which demonstrates the efficiency or nonefficiency of the collateral cerebral circulation, is all important in avoiding disaster following immediate total ligation of this vessel.

After partial ligation of this vessel (with fascial bands) a later total occlusion can be safely performed in one to two weeks, or even less.

The great danger in partial occlusion is in obliterating the lumen too far. If cerebral signs develop during the succeeding six or eight hours, the band can be removed, and at times the cerebral circulation will be restored.

For total ligation of this vessel an interposed fascial band is probably the best assurance against thrombosis and the resulting late cerebral complications.

Clipping the internal carotid artery intracranially is relatively safe and easy and is essential in treating many intracranial aneurysms.

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# INFLUENCE OF HYPOPHYSECTOMY ON THE EPITHELIZATION OF WOUNDS AND ON FIBROPLASIA

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AND

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ST. LOUIS

Wound healing, a thoroughly fundamental biologic problem, has been subjected to a great deal of investigation with the production of many methods of attack and many sets of results often at variance with each other. The factual observation of healing has been carefully carried out and recorded, while the causative agents and the modifying stimuli have been less well explained. The capacity to repair injury in a tissue decreases with increasing specialization of that tissue, and in highly specialized structures substitutive repair by means of fibroplasia occurs, while epithelium retains the ability to repair denuded surfaces. It is the purpose of this paper to study what effect the removal of the hormones of the pituitary and of those glands under the control of the pituitary has on the ability of an animal to exert reparative epithelial growth or reparative fibroplasia.

The investigations of Loeb<sup>1</sup> opened the way for modern studies of epithelization by demonstrating that the squamous cells of the external epithelium possess the property of ameboid movement, which is called into play whenever denudation occurs and that by the formation of epithelial tongues closure is primarily effected. Loeb<sup>2</sup> subsequently classified the various mechanisms of wound healing as increases in ameboid movement, in mitosis, in cell size, in thickness of the stratum germinativum, in the number of cell rows and in the number of cells. All but the first reach maximum intensity at the time of closure; ameboid movement is most active in the early stages of epithelization. These fundamentals have been confirmed by Carrel, Burrows, Arey, Herrick

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From the Department of Surgery, Washington University School of Medicine, and Barnes Hospital.

1. Loeb, L.: Ueber Regeneration des Epithels, Arch. f. Entwcklgsmech. d. Organ. 6:297, 1898.

2. Loeb, L.: A Comparative Study of the Mechanism of Wound Healing, J. M. Research 41:247, 1920.

and Holmes. Carrel, however, emphasized the importance of the latent period and the granular retraction period before epithelial migration occurs.

The factors involved in the establishment of a healing response have been studied extensively. Loeb was convinced of the importance of the role of the wound as a foreign body in stimulating the ameboid activity of the epithelial cells much as a microscopic foreign body might stimulate the more active leukocytes into ameboid movement. Carrel<sup>3</sup> investigated the role that irritants play in initiating contraction of the wound and the role that embryonic tissue juices play in fibroplasia and emphasized the fibroplastic character of cicatrization. Altered metabolism and degenerative products of tissue destruction were observed by Kornfeld<sup>4</sup> to increase wound healing. The diminution in the size of epithelial wounds was studied by Burrows,<sup>5</sup> who concluded that stagnation of circulation is the stimulus to repair. Similar methods were used by Lauber,<sup>6</sup> who observed that parenteral injections of gonadotropin ("prolan") and of posterior pituitary extract increase the rate of cicatrization, that androgens are effective in subjects of both sexes and that estrogens are especially efficacious in female subjects. Ceccarelli<sup>7</sup> concluded that local application of anterior pituitary extract increases the initial response but does not shorten the total healing time.

Lauber<sup>8</sup> and others found that various administrations of thyroid extract reduce the healing time of skin lesions in the rat by almost 50 per cent. Many workers have found that administration of testis and thyroid pulp, either by direct application to the wound, by subcutaneous injection or by oral administration has resulted in the acceleration of healing. Surgical removal of the gonads, however, does not influence healing, though resection of the thyroid and the parathyroids was said by Kosdoba<sup>9</sup> and others to cause retardation of wound healing; implantation

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3. Carrel, A.: Cicatrization of Wounds: XII. Factors Initiating Regeneration, *J. Exper. Med.* **34**:425, 1921.

4. Kornfeld, W.: Ueber den Zellteilungsrythmus und seine Regelung, *Arch. f. Entwcklgsmech. d. Organ.* **50**:526, 1922.

5. Burrows, M. T.: Studies on Wound Healing: I. First Intention Healing of Open Wounds and the Nature of the Growth Stimulus in the Wound and Cancer, *J. M. Research* **44**:615, 1924.

6. Lauber, H. J.: Experimentelle Untersuchungen über die Beziehungen der innersekretorischen Drüsen zur Wundheilung, *Beitr. z. klin. Chir.* **157**:244, 1933.

7. Ceccarelli, G.: Sul problema della rigenerazione: influenza del sistema endocrino nella rigenerazione della pelle e delle ossa, *Arch. ital. di chir.* **27**:641, 1930.

8. Lauber, H. J.: Innere Sekretion—Infektionsbereitschaft und Wundheilung. *München. med. Wchnschr.* **77**:434, 1930.

9. Kosdoba, A. S.: Wundheilung und Schilddrüse, *Arch. f. klin. Chir.* **179**: 551, 1934.

may or may not accelerate healing. Direct application of adrenal gland or injections of epinephrine were observed by Lauber and others to shorten healing time. Other workers, including Kosdoba,<sup>10</sup> found that attempts to stimulate the adrenal gland result in lengthening the healing time.

The importance of fibroblastic proliferation in the healing of wounds of all types is well recognized, and many attempts have been made to find some factor which will modify the rate of fibroplasia in the hope of affecting wound healing. Extensive studies by Carrel and Ebeling<sup>11</sup> on the growth of fibroblasts in vitro led them to the conclusion that embryonic tissue juices contain a substance which stimulates and prolongs the multiplication of fibroblasts. This coincided with the observation by Du Nouy<sup>12</sup> that the healing rate in human beings is related to the age of the persons, and mathematical formulas were derived showing that the rate of fibroplasia decreases with increasing age. Howes and Harvey<sup>13</sup> showed that the rate of fibroplasia in young and adult rats is the same but that in the young animals the latent period is shorter and that there is less retardation of growth when healing is nearly completed than in adult rats. Howes, Sooy and Harvey<sup>14</sup> plotted curves of the tensile strength of healing wounds and correlated the recovery of strength with the fibroblastic activity. Howes and associates<sup>15</sup> found that dietary deficiency in adult rats has no effect on wound healing but definitely retards healing in young rats. Hammett<sup>16</sup> observed that sulfhydryl increases the number of mitoses in onion root tip and expressed the opinion that the growth-accelerating influence acts to increase the number of mitoses but not to increase the cell size. Hammett and Reimann<sup>17</sup> noted that the presence of the sulfhydryl radical as thioglucose speeds healing of

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10. Kosdoba, A. S.: Ueber den Einfluss der Nebennieren auf die Wundheilung, Arch. f. klin. Chir. **179**:435, 1934.

11. Carrel, A., and Ebeling, A. H.: The Multiplication of Fibroblasts in Vitro, J. Exper. Med. **34**:317, 1921.

12. Du Nouy, P. L.: Mathematical Expression of the Curve Representing Cicatrization, J. Exper. Med. **24**:451, 1916.

13. Howes, E. L., and Harvey, S. C.: The Age Factor in the Velocity of the Growth of Fibroblasts in the Healing Wound, J. Exper. Med. **55**:577, 1932.

14. Howes, E. L.; Sooy, J. W., and Harvey, S. C.: The Healing of Wounds as Determined by Their Tensile Strength, J. A. M. A. **92**:42 (Jan. 5) 1929.

15. Howes, E. L.; Griggs, H.; Shea, R., and Harvey, S. C.: Effect of Complete and Partial Starvation on the Rate of Fibroplasia in the Healing Wound, Arch. Surg. **27**:846 (Nov.) 1933.

16. Hammett, F. S.: The Chemical Stimulus Essential for Growth by Increase in Cell Number, Protoplasma **7**:297, 1929.

17. Hammett, F. S., and Reimann, S. P.: Cell Proliferation Response to Sulfhydryl in Mammals, J. Exper. Med. **50**:445, 1929.

skin wounds in rats, and Reimann<sup>18</sup> reported satisfactory healing of chronic ulcers in human beings, although granulations were excessively proliferative. Carrel<sup>19</sup> observed that irritants decrease the latent period and cause more rapid completion of epithelization in skin wounds of dogs. Voronoff and Bostwick<sup>20</sup> found that adrenal pulp applied directly to wounds produces thick granulations.

The object of this study was to determine what effect the withdrawal of pituitary hormones and of the secretion of the glands under pituitary control has on the epithelization of skin wounds and on the strength of wounds healing by fibroplasia.

#### MATERIALS

Normal young adult rats of the Wisconsin strain were used in this experiment. They were fed a diet of Purina dog chow and kept isolated during the course of the experiment. The Purina dog chow consisted of protein 22.5 per cent, fat 5.5 per cent, carbohydrate 50.25 per cent, fiber 3.75 per cent and ash 7 per cent. The calcium-phosphorus ratio was 1.75:1. Each gram contained 8.5 U. S. P. units of vitamin A and 2.3 U. S. P. units of vitamin D. The concentration of thiamine hydrochloride was 4 parts per million, of riboflavin 4.75 parts, of pantothenic acid 10 parts and of niacin 35 parts. The animals were between 20 and 26 weeks old when used in the experiment, and hypophysectomy had been performed when they were 14 to 16 weeks old. Criteria for completeness of hypophysectomy were: 10 per cent loss in weight, loose thin skin, fine silky hair, emaciation, atrophy of the testes in the males and, seen post mortem, atrophy of the gonads, the adrenal and the thyroid glands. Inspection of the base of the brain made certain that no bit of pituitary was left.

#### EPITHELIZATION

In the first part of the experiment the reparative properties of epithelium of the skin were studied with 18 normal and 19 hypophysectomized rats.

With the animals under anesthesia induced with soluble pentobarbital and ether, a skin flap 2 sq. cm. in area was resected from the right flank, and the animal was placed in a clean individual cage. In 2 normal animals there was superficial wound infection. These animals were discarded. On the first and every other subsequent day, the wound area was traced on cellophane and measured by means of a planimeter. The size of the original wound in the normal rats averaged slightly larger than in the hypophysectomized animals, owing perhaps to looseness of the skin and greater stretching before marking in the hypophysectomized rats and a greater degree of elasticity in the connective tissue of the normal animals.

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18. Reimann, S. P.: Use and Reasons for the Use of Thiocresol to Stimulate Wound Healing, *J. A. M. A.* **94**:1369 (May 3) 1930.

19. Carrel, A.: Cicatrization of Wounds: XII. Factors Initiating Regeneration, *J. Exper. Med.* **34**:425, 1921.

20. Voronoff, S., and Bostwick, E.: Accélération intensive de bourgeonnement des plaies par l'application de pulpe testiculaire, *Compt. rend. Acad. d. sc.* **167**:385, 1918.

The average wound was 2.06 sq. cm. in the 18 normal rats and 1.87 sq. cm. in the 19 hypophysectomized rats. On the fourth day, the wounds were approximately equal in size, 1.16 and 1.22 sq. cm., respectively, and the curves of healing were similar until complete healing was obtained on the seventeenth day (chart 1).

This part of the experiment had been divided into two parts. In 10 normal and 8 experimental animals the 2 sq. cm. was of rectangular shape, and in 8 normal and 11 experimental animals the wound was of circular shape. The original area and curves of healing were identical in both groups, and they have been combined.

In 2 animals, not included in the results already given, the wound became infected. The resulting cicatrices were larger than those of the rest of the animals and showed the effect of abundant fibroblastic granu-

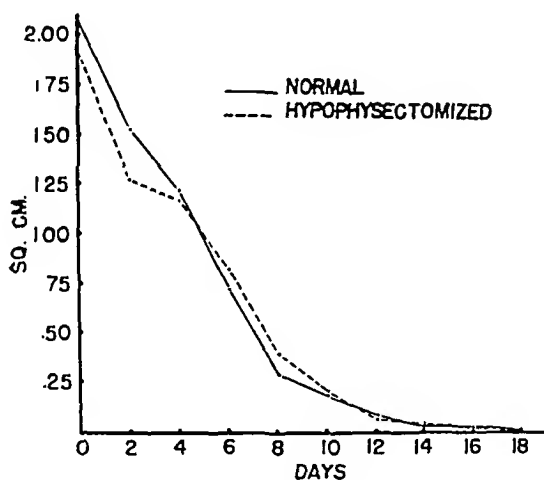


Chart 1.—Curves showing decrease in area of healing wounds on the right flanks of normal and hypophysectomized rats.

lations in the base of the wound. Complete healing in these cases occurred on the eighteenth and twenty-first days.

#### FIBROPLASIA

In the second part of the experiment the reparative properties of fibroplasia were studied in 27 normal and 19 hypophysectomized rats.

After ten hour fasting, with the animals under anesthesia induced with soluble pentobarbital and ether, an incision 2 cm. long was made through the left rectus muscle. The stomach was delivered, and a 1 cm. incision was made. This was closed with no. 000 plain catgut by a running mattress suture through the serosa and the muscularis. The abdominal wound was closed with fine silk, and the animal was permitted to eat and drink as soon as it wished after recovering from the effects of narcosis.

To determine healing of the wound a method similar to that developed by Harvey<sup>21</sup> was used. The rat was killed with chloroform and immediately opened, and the esophagus and the fundus of the stomach were tied off. A large cannula was inserted through the pylorus and tied in place. A mercury manometer on the air supply line indicated the pressure in the stomach. Air was introduced slowly, so that the rise in pressure was approximately 100 mm. of mercury per minute. Attempts were made to record pressure rises on a kymographion, but the friction and the weight of the system caused appreciably low results, so this was dispensed with, and the mercury column was watched closely to obtain the real pressure. During inflation of the stomach to the breaking point, the organ was kept moist by warm solution of sodium chloride.

Fibroplasia as measured by the return of strength in the healing wound occurred from the fourth to the eighth day, when the wound was

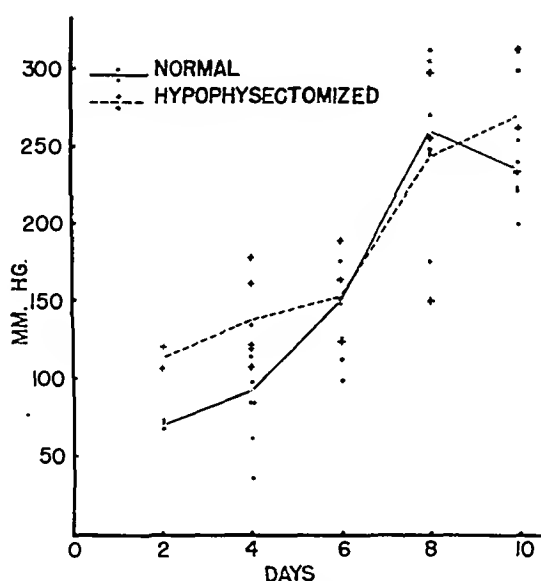


Chart 2.—Curves showing the return of strength in wounds of the stomachs of normal and hypophysectomized rats as measured by the method of introducing air under pressure until the wound breaks.

as strong as the stomach itself, and in 50 per cent of the cases in which tests were made at the eighth day, the rupture occurred in the stomach wall and not at the wound. Analysis of the curves of healing obtained from the two groups of animals shows that the average strength of the wounds of the hypophysectomized animals on the fourth day was about 50 per cent greater than that of the controls. This tendency for the experimental animals to have wounds that were stronger than the normal animals was seen also at the second day when a wide difference appeared.

21. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, *Ann. Surg.* **91**:641, 1930.

However, on the sixth day postoperatively there was no difference, and on the eighth day also, the strength of the wounds in the two groups was still the same, though in this case some of the wounds were not measured directly, since the stomach wall broke before the wound did. The curves of healing are shown in chart 2. These curves have the S shape which is so generally found in all biologic growth.

#### COMMENT

These results indicate that ameboid movement of the epithelium of the skin is not affected by the absence of various hormones of the pituitary or of secretions from any endocrine glands under the control of the pituitary. Tissue culture work of Carrel, Baker, Burrows, Holmes and others also showed that epithelium has ameboid motion in the absence of hormonal influence.

Lauber found that injections of posterior pituitary extract and gonadotropin decreased the healing time of skin wounds from twenty-two days to fourteen or sixteen days. He noted that androgens reduced healing time by eight days in male rats and three days in female animals and that estrogens reduced healing in female rats from twenty-two to twelve days but were ineffective in male animals. Di Natale and Midana <sup>22</sup> said that removal of the gonads has no effect on healing, but Merlini <sup>23</sup> reported that transplantation of the testis has a favorable effect. Kosdoba found an increase in healing following the use of thyroid extract; he attributed this to an influence on the connective tissue and the vascular tissue as well as to some alteration of the biochemical nature of the wound itself. However, in hypophysectomized animals with demonstrably low basal metabolic rates and atrophic gonads, we observed no alteration in the rate of epithelization or fibroplasia.

Lauber noted a six day decrease in the healing time after injecting epinephrine, and Santorsola <sup>24</sup> found changes after unilateral adrenalectomy leading to decreased rate of healing proportional to the time elapsing after ablation of the gland. We observed no decrease in healing even with complete atrophy of the adrenals following hypophysectomy.

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22. di Natale, L., and Midana, A.: Ricerche sperimentali sulla influenza della tiroide, del testicolo e dell' ovaio nel processo di cicatrizzazione delle ferite, *Poli-clinico (sez. chir.)* **38**:21, 1931.

23. Merlini, A.: Sulla influenza della tiroide e delle ghiandole sessuali nel processo de cicatrizzazione delle ferite, *Endocrinol. e. patol. costit.* **3**:174, 1928.

24. Santorsola, D.: Influenza delle capsule surrenali sul trofismo: La guarigione delle piaghe asettiche negli animali monosurrenalectomizzati, *Pathologica* **23**:463, 1931.

Though tissue changes make the skin loose and flabby, this does not affect movement of the epithelium.

Harvey<sup>25</sup> observed that fibroplasia in healing wounds starts out with maximum velocity and that the curves of healing that he obtained did not show an initial lag period but were the autokinetic or retardation phase of the typical S-shaped curve of biologic growth. The lag period in our curves may be either a true lag period or only the measurement of residual strength added to the wound by sutures holding the wound closed. We are not prepared to say which of these possibilities is correct.

#### SUMMARY

Skin over an area of 2 sq. cm. on the right flank of 18 normal and 19 hypophysectomized young adult rats was resected; the animals were isolated; the wound was measured by means of cellophane and a wax pencil, and the area was calculated with a planimeter. There was no difference in the epithelization time of the wounds in the two series of animals.

In the stomachs of 29 normal and 18 hypophysectomized rats, an incision 1 cm. long was made and sutured with no. 000 plain catgut. At varying intervals after operation, air was introduced into the stomach under measured pressure, and the pressure at which the wound broke was recorded (Harvey's method). The curves of healing of the two groups of animals were essentially similar in the phase of greatest fibroblastic activity and most rapid return of strength. During the initial lag phase the wounds of the hypophysectomized animals were slightly stronger than those of the normal animals. We are unable to explain this.

#### CONCLUSIONS

Hypophysectomy causes no change in the rate of epithelization of skin wounds or of fibroblastic repair of stomach wounds in the rat.

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25. Harvey, S. C.: The Velocity of the Growth of Fibroblasts in the Healing Wound, *Arch. Surg.* **18**:1227 (April) 1929.



# ADENOMA OF THE BRONCHUS WITH SUCCESSFUL PNEUMONECTOMY

## REPORT OF A CASE

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Prior to 1928<sup>1</sup> little was known concerning the clinical and pathologic aspects of benign polypoid epithelial tumors of the bronchus. These were frequently thought to be atypical carcinoma. Clinically, many patients with such tumors were considered as having diverse forms of bronchopulmonary disease and were consequently subjected to incorrect and often protracted forms of treatment. In recent years a better understanding of these tumors has been brought about by the development of bronchoscopy, advances in thoracic surgery and clinicopathologic studies. A number of excellent investigations during the last decade have shown this group of bronchial tumors to be fundamentally benign and amenable to surgical treatment.

The following case illustrates many of the characteristics of this particular type of lesion.

## REPORT OF CASE

Mrs. C. G., a 22 year old white woman, entered The Dalles Hospital on May 25, 1938, for treatment of a chronic lung abscess. On two occasions (at 1 and 7 years of age, respectively), a diagnosis of pneumonia involving the right lung had been made. For three years after the last attack of "pneumonia" she was "never well," but between the ages of 10 and 12 she began to feel better. When 12, she had her first pulmonary hemorrhage. From then to the time of admission to the hospital she had an average of two to four hemorrhages per month. These bouts of hemoptysis invariably occurred in the same manner. A rise in temperature to approximately 102 F. first occurred; the fever usually lasted three days and was followed and terminated by a sudden evacuation of blood and, later, of pus. When 16, she married and soon became pregnant. At the time of delivery she was in a critical state because of repeated hemorrhages from the lungs. Following the birth of her child she lost weight rapidly and at the age of 17 entered the

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1. Reisner, D.: Intra-Bronchial Polypoid Adenoma, Arch. Surg. **16**:1201-1213 (June) 1928.

Eastern Oregon State Tuberculosis Hospital with a diagnosis on admission of pulmonary tuberculosis. This diagnosis was not confirmed during the six months of hospitalization. It was felt, however, that she suffered from a lung abscess on the right side. Phrenectomy was done, and she was treated with autogenous vaccine. When dismissed, she was only slightly improved, and the intermittent hemorrhages continued. From January to April 1938 she had three to four hemorrhages per month, always with preceding fever lasting from four to five days. At the end of this time hemorrhage and evacuation of pus would relieve her, but the cycle would reappear in a week or ten days. In April 1938 she consulted Dr. James Odell, of the Eastern Oregon State Tuberculosis Hospital, who confirmed the clinical diagnosis of pulmonary abscess and referred the patient to one of us (T. C.) for treatment.

*Course.*—Stereographic roentgenograms with and without iodized poppyseed oil showed the middle and lower lobes of the right lung practically destroyed and



Fig. 1.—Photograph of the primary intrabronchial tumor. The dark streaks represent the vascular areas.

riddled with what were interpreted as numerous abscess cavities. Pneumothorax was instituted and maintained for three weeks. On May 26, with the patient under anesthesia induced with amylene hydrate and ether, thoracotomy was performed through the seventh intercostal space. At operation the collapsed lower and middle lobes were dissected free from adhesions attached to the parietal pleura, the mediastinal structures and the diaphragm. The many dense adhesions over the upper lobe also were severed. It was found impossible to separate the superior lobe from the carnified middle one because of extensive interlobar fibrosis. At this time a hard tumor mass was palpated in the hilar portion of the lung. Then, because of the patient's poor condition, the wound was loosely closed, and she was returned to her room. Her postoperative condition progressed satisfactorily, and on June 2, seven days later, the thoracotomy wound was opened and pneumonectomy performed. When the hilar structures were cut across during the removal of the

lung a smooth, round, apparently unattached tumor fell out of the severed bronchus. After the operation she was given three blood transfusions and by June 28 was able to be out of bed. Her further hospital course was uneventful. One year later the patient had put on considerable weight and was doing her own housework without difficulty. During this time she had been free of all previous symptoms. Of interest is the fact that during the summer of 1941 she ascended Mt. Adams (in the state of Washington; elevation 12,307 feet [3,749.8 meters]) with one lung. On March 10, 1942, she was found to be of normal weight and in excellent health.

*Macroscopic Observations.*—A small rounded tumor and the entire lung were received as separate specimens. The tumor (fig. 1) measured 3 by 4 by 3.2 cm. in diameter. It was covered by a thin translucent grayish capsule through which the

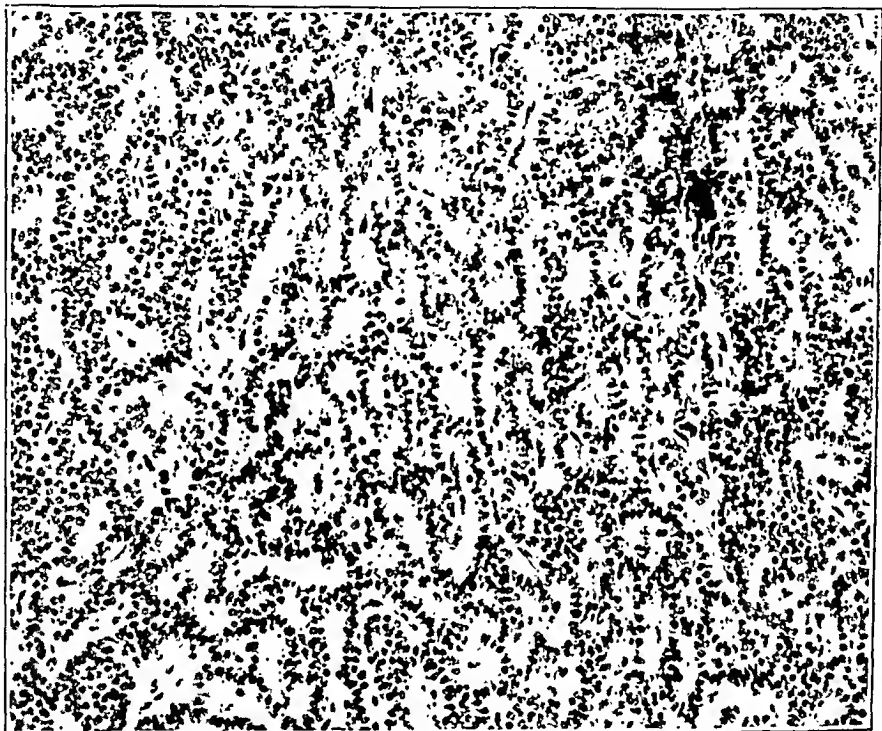


Fig. 2.—Photomicrograph showing the alveolar grouping of the cells ( $\times 164$ ).

underlying tissue appeared brownish yellow to red. At one point there was a small flat defect (1.5 by 1.0 cm.) in the capsule; this possibly represented the attachment point of a pedicle. On section the presenting surfaces were found to be uniformly firm and of rubbery consistency. The bulk of the tissue consisted of pale, yellowish to grayish white cellular-appearing material. There were irregular serpiginous streaks coursing through the growth that appeared red to brown.

All lobes of the lung were diminished in size. The upper lobe was moderately air containing throughout. The lower and middle lobes were firm, solid and greatly contracted. At the hilus extensive dilatation of the main stem bronchus was noted. Here, just proximal to its division into upper and lower bronchi, the lumen measured 3 by 2.5 cm. in diameter. The wall at this point was thin and measured from 1 to 1.5 mm. in thickness. Cartilaginous rings were not observed here, nor was a

pedicle found to which the tumor might have been attached. A sagittal section of the lower and middle lobes 1.5 cm. lateral to this region revealed the main bronchi surrounded by contracted hard yellowish white tissue. The lumens of the bronchi here varied from 7 to 5 mm. in diameter. The middle lobe was atelectatic, was not air containing and showed no evidence of bronchiectasis or fibrosis. In the lower lobe normal lung tissue was replaced by fibrous-appearing tissue. The lining walls of the bronchi here were slightly thickened and discolored grayish brown. The interlobar pleura was indurated and thickened. No gross evidence of tumor was found in the lung or the bronchi. There was no evidence of lung abscess.

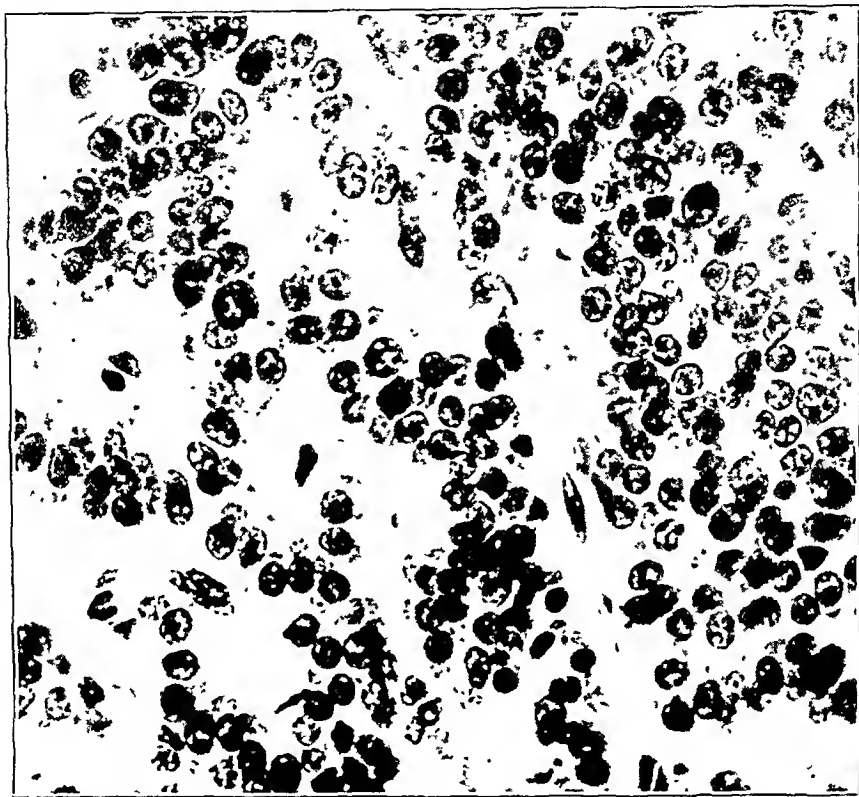


Fig. 3.—Higher power photomicrograph of the specimen shown in figure 2 ( $\times 660$ ).

*Microscopic Observations.*—Sections of the bronchial tumor, the bronchi and the upper and lower lobes of the lung revealed the following changes: In the blocks of bronchial tumor ciliated columnar epithelium was seen covering the surface of the growth. This epithelial layer was intact and well differentiated. Beneath the covering epithelium a thin layer of fibrous tissue existed, separating this epithelium from tumor cells beneath. The latter cells in most areas exhibited an alveolar pattern (fig. 2). The spaces thus formed were bordered by medium-sized to small, round and oval cells. Cell nuclei were invariably round to oval and of constantly and uniformly small size (fig. 3). They often contained small particles of chromatin. In no instances were mitoses noted. The cytoplasm were ill defined



Fig. 4.—Photomicrograph showing the large thyroid-like alveoli filled with erythrocytes ( $\times 164$ ).

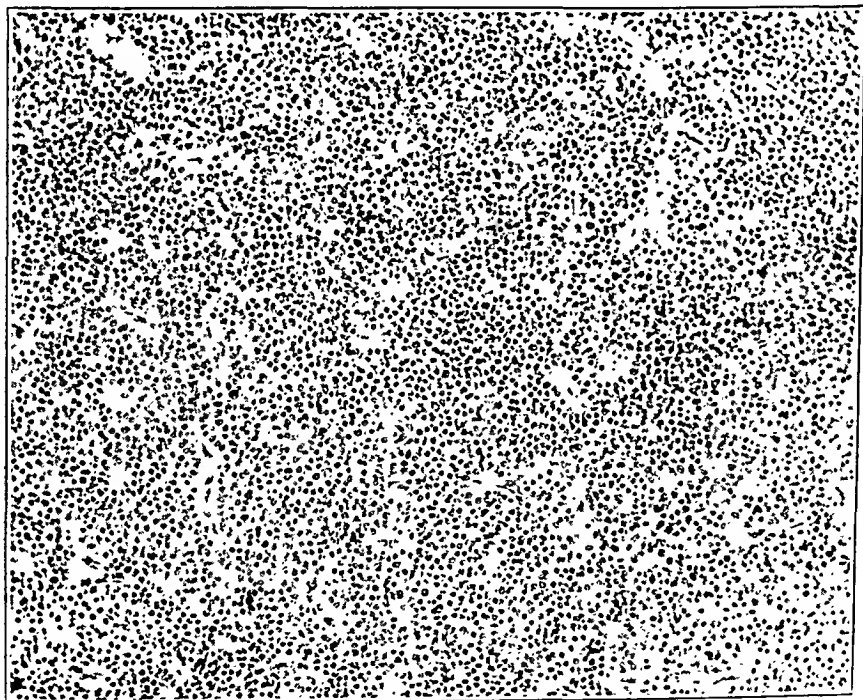


Fig. 5.—Photomicrograph showing cells in diffuse distribution.

and scant. In most areas the supportive stroma was delicate and consisted only of one or two minute strands of fibrous tissue through which an occasional capillary coursed. In some zones (fig. 4) the supportive tissue assumed a clear structureless appearance and looked not unlike that seen in some fetal adenomas of the thyroid gland. In still other areas of the tumor alveolar structures were absent (fig. 5), and the cells were closely placed and formed solid diffuse sheets. Sections of the thinned bronchial wall wherein the tumor lay showed the lining epithelium destroyed and cartilage and mucous glands absent. Only mildly inflammatory fibrous tissue remained.

In the lower lobe of the lung air cells and alveoli were replaced by dense fibrous tissue within which a few regenerative alveolar epithelial cells were noted. Here also were found dilated bronchioles lined by hyperplastic epithelium, often exhibiting considerable papillary infolding. The submucosa of these projections was heavily infiltrated with lymphocytes and increased numbers of polymorphonuclear eosinophils. Within the lumens polymorphonuclear neutrophil cells were present in large numbers. The arteries in this consolidated lobe showed thickening of the intima and extreme narrowing of the lumens but no thrombosis.

*Pathologic Diagnosis.*—The pathologic diagnosis was benign papillary adenoma of the bronchus producing pressure atrophy of the bronchial wall with purulent bronchiectasis and carnification of the lower and middle lobes.

#### COMMENT

In contradistinction to bronchogenic carcinoma this interesting type of bronchial tumor occurs relatively early in life. The average age of patients whose cases are reviewed in the literature at the onset of symptoms is fairly consistent. Various investigators have recorded the following data: Brunn and Goldman,<sup>2</sup> 14 cases, in which the average age was 27 years; Jackson and Konzelmann,<sup>3</sup> 12 cases, in which the average age was 31 years; Graham and Womack,<sup>4</sup> 11 cases, in which the average age was 32 years; Wessler and Rabin,<sup>5</sup> 10 cases, in which the average age was 32 years. Of 9 cases studied at the Massachusetts General Hospital, Boston,<sup>6</sup> in 8 the patients were persons varying in age from the late teens to the late twenties. Differing sharply from instances of malignant bronchial neoplasms, in which roughly 8 male patients are affected to 1 female patient, this tumor occurs more fre-

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2. Brunn, H., and Goldman, A.: The Differentiation of Benign from Malignant Polypoid Bronchial Tumors, Surg., Gynec. & Obst. **71**:703-722 (Dec.) 1940.

3. Jackson, C. L., and Konzelmann, F. W.: Bronchoscopic Aspects of Bronchial Tumors with Special Reference to Bronchial Adenomas, J. Thoracic Surg. **6**:312-329 (Feb.) 1937.

4. Womack, N., and Graham, E.: Mixed Tumors of the Lung, Arch. Path. **26**:165-206 (July) 1938.

5. Wessler, H., and Rabin, C.: Benign Tumors of the Bronchus, Am. J. M. Sc. **183**:164-180 (Feb.) 1932.

6. Adenomata of the Bronchus, Cabot Case 22231, New England J. Med. **214**: 1149-1157 (June 4) 1936. Adenoma of the Bronchus, *ibid.* **214**:1153-1157 (June 4) 1936.

quently in female patients. In 70 per cent of 60 cases reviewed in the literature <sup>7</sup> the patients were found to be women.

The most consistent symptoms are those related to the local bronchial lesion. Of these, cough and hemoptysis are the most common early complaints. Later, pain in the chest, shortness of breath and fever are complained of in that order of frequency. These symptoms are related to secondary changes occurring in the bronchi, the lungs and the part of the pleura distal to the tumor. The most frequent secondary alterations are atelectasis, bronchiectasis, diffuse pneumonitis, abscess and empyema.

Symptoms have often been present for several years when the patients are first seen. Graham and Womack <sup>4</sup> reported 3 cases in which symptoms were present for over twenty years. Wessler and Rabin <sup>5</sup> observed an instance of adenoma of the bronchus in a 64 year old man who had had symptoms for thirty years. As illustrated in our case, suddenness of onset and termination of pulmonary hemorrhage is often characteristic of this type of tumor. The extreme vascularity of the tumors no doubt accounts for the frequency and the severity of the bleeding. Because of this sign often associated with fever it is not difficult to see how our case and many others were initially and erroneously thought to be instances of pulmonary tuberculosis. In Goldman's series of 18 cases <sup>8</sup> a previous diagnosis of pulmonary tuberculosis had been made in 6.

Some controversy exists regarding the origin of these tumors. Rabin was first quoted <sup>9</sup> as stating that they originate from epithelial cells of the ducts of the bronchial mucous glands. Konzelmann <sup>3</sup> was not convinced of this theory. Later Graham and Womack <sup>4</sup> stated that they considered the entire group of benign bronchial tumors (adenoma, fibroma, chondroma, etc.) to be derived from one or two germinal layers (mesoderm and entoderm) and considered them as mixed tumors analogous to those occurring in the salivary glands. In reviewing the bronchial tree from the embryologic point of view, they said that incom-

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7. (a) Zamora, A. M., and Schuster, N.: Vascular Adenoma of the Bronchus, *J. Laryng. & Otol.* **52**:337-343 (May) 1937. (b) Gower, F. J. S.: Adenoma of the Bronchus, *Proc. Roy. Soc. Med.* **30**:673-680 (April) 1937. (c) Laff, H. I.: Benign Tumors of Bronchi with Special Reference to Vascular Adenoma, *Arch. Otolaryng.* **31**:148-159 (Jan.) 1940. (d) Hart, V. K.: Report of Four Interesting Bronchoscopic Cases, *Tr. Am. Laryng., Rhin. & Otol. Soc.* **43**:380-398, 1937. (e) Brunn and Goldman.<sup>2</sup> (f) Jackson and Konzelmann.<sup>3</sup> (g) Womack and Graham.<sup>4</sup> (h) Wessler and Rabin.<sup>5</sup>

8. Goldman, A.: Polypoid Bronchial Tumors with Special Reference to Bronchial Adenomata, *California & West. Med.* **53**:123-127 (Sept.) 1940.

9. Kramer, R.: Adenoma of Bronchus, *Ann. Otol., Rhin. & Laryng.* **39**:689-685 (Sept.) 1930.

plete development, defect of axial formation or tissue orientation may give rise to deformed areas ultimately resulting in the formation of a tumor. The not infrequent observation<sup>10</sup> of islets of cartilage in some of these neoplasms is a point in favor of the latter theory regarding the basic nature of the growths.

The position and the appearance of the tumor were well described by Brunn and Goldman<sup>2</sup> and by Jackson and Konzelmann.<sup>3</sup> The first-named authors showed that there are three fundamental positions of the growths: endobronchial, those wholly within the bronchus; intramural, those protruding into the bronchus but having a larger intramural part; extraendobronchial, those within the bronchus but having a larger adjacent extrabronchial part. During life by direct observation they are movable, soft, fleshy, pinkish or purplish and polypoid in shape. The surfaces are usually smooth and rarely ulcerated. The bronchoscopic appearance of the tumor in 12 cases was well shown by the drawings included in the article by Jackson and Konzelmann.

The histologic picture in this case was fairly characteristic of tumors of this type. Reports of various investigators<sup>11</sup> revealed the tumors to have a consistent structure and to be invariably composed of small round cells having deeply stained nuclei and scant cytoplasm. They are arranged in round and oval alveoli separated by scant vascular connective tissue stroma. The vascularity often forms such a prominent part of the histologic appearance that the neoplasms are occasionally confused with hemangiomas. In 4 of the 5 cases described by Zamora and Schuster<sup>7a</sup> large blood-filled capillaries and sinuses constituted a prominent feature of the lesions. Mitotic figures are characteristically absent, although Gowar<sup>7b</sup> and Reisner<sup>1</sup> listed occasional ones present in their material. Variations in the structure and the arrangement of the tumor cells as found in different parts of our tumor were also described by Graham and Womack.<sup>4</sup> Reisner<sup>1</sup> and Fried<sup>12</sup> called attention to their observations that the tumor cells are occasionally columnar or bear a close resemblance to mucous gland cells.

Different views exist regarding the malignant or the nonmalignant nature of the neoplasms. Graham and Womack<sup>4</sup> expressed the belief that they are potentially malignant and stated that they have observed 1 patient in whom the mediastinal lymph nodes were involved. Necropsy studies of Kramer and Som<sup>13</sup> showed no regional or distant metastases

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10. Goldman, A.: Personal communication to the authors.

11. Reisner.<sup>1</sup> Jackson and Konzelmann.<sup>3</sup> Womack and Graham.<sup>4</sup> Wessler and Rabin.<sup>5</sup> Zamora.<sup>7a</sup> Gowar.<sup>7b</sup>

12. Fried, B. M.: Adenoma of Bronchial Mucous Glands, *Arch. Otolaryng.* **20**:375-381 (Sept.) 1934.

13. Kramer, R., and Som, M. L.: Further Study of Adenoma of Bronchus, *Ann. Otol., Rhin. & Laryng.* **44**:861-878 (Sept.) 1935.



in 5 cases. Jackson and Konzelmann<sup>3</sup> expressed the opinion that the tumors are benign but capable of malignant transformation. At the time their report was published none of their 12 patients had died so the true extent of the individual lesions was actually unknown. In 1932 Wessler and Rabin<sup>5</sup> presented abstracts of 12 cases. In 4 of these necropsy was performed. In 3 of the 4 no mention was made of the presence or the absence of mediastinal involvement. In the fourth case it was stated that no extensions or metastases were observed. In this same communication 2 additional cases thought to be cases of carcinoma arising in preexisting adenoma were described. The descriptions did not mention the presence or the absence of near or distant metastases, nor were photomicrographs of the growths presented. It is unfortunate that evidence supporting their contention was not presented, particularly so in that so little information is at hand regarding the transformation of adenoma to a malignant lesion. Goldman<sup>10</sup> stated that necropsy in 4 cases and surgical tissue examinations (lobectomy, pneumonectomy) in 4 others failed to show metastases but that local infiltration was found in several. From what has been noted one appreciates the controversial status of these tumors. It appears that the clinical and pathologic characteristics described to date are those more commonly associated with benign tumors. The reports of rare cases in which adenoma changed to carcinoma or mediastinal lymph node metastasis was exhibited are incomplete and give the reader no convincing proof of such occurrences. It may be that future observations will demonstrate more thoroughly that these growths are capable during some stage of their evolution of acquiring malignant characteristics.

In the experience of Brunn and Goldman<sup>2</sup> roentgen treatment did not improve symptoms or change the structure of the tumors. Bronchoscopic removal is indicated for those persons not having irreversible pulmonary changes. Otherwise lobectomy or pneumonectomy is the procedure of choice.

#### SUMMARY

An instance of adenoma of the bronchus occurring in a 22 year old woman is presented.

Pneumonectomy effected complete relief of symptoms, and nearly four years later her general health was excellent.

The age and the sex incidence, the symptoms and the pathologic aspects are discussed.

It is emphasized that evidence is lacking regarding the capability of this form of tumor to become malignant.

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# ADMINISTRATION OF DICOUMARIN COMPOUND\* FOR PROPHYLAXIS OF POSTOPERATIVE THROMBOSIS AND EMBOLISM

## A PRELIMINARY REPORT

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The practical value of the use of an agent to prolong the clotting time of the blood in the prophylaxis and treatment of thromboembolic disease has been amply demonstrated. Administration of an anticoagulant, such as heparin, has been found to be safe for operative patients immediately after<sup>1</sup> or even before operation.<sup>2</sup> Heparin has reduced the expected occurrence of thrombosis and embolism in operative patients.<sup>1</sup> It has served well in the management of patients with nonfatal pulmonary embolism.<sup>1</sup> It has materially reduced the morbidity rate associated with thrombophlebitis.<sup>1</sup> The principles of its use have been established. But two factors, the expense and the comparative difficulty of administration, have tempered the enthusiasm for heparin and prevented its acceptance as a measure available to all. For this reason the results of the use of another anticoagulant, dicoumarin compound, 3,3'-methylenebis-4-hydroxycoumarin,<sup>3</sup> have been studied in order to explore its possibilities for routine administration.

Dicoumarin compound requires twenty-four to forty-eight hours to produce its characteristic effect of prolongation of the prothrombin and clotting times of the blood, depending on individual reactions to the drug. Therefore, if its anticoagulant action is to be fully available in the protection of the patient from postoperative thrombotic complications, it

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\* 3,3'-methylenebis-4-hydroxycoumarin.

The dicoumarin compound used in this study was furnished by the Abbott Laboratories.

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1. Murray, G.: Heparin in Thromboses and Blood Vessel Surgery, Surg., Gynec. & Obst. **72**:340-344 (Feb.) 1941.

2. Butsch, W. L., and Stewart, J. D.: Unpublished data.

3. Stahman, M. A.; Huebner, C. F., and Link, K. P.: Hemorrhagic Sweet Clover Disease: Identification and Synthesis of Hemorrhagic Agent, J. Biol. Chem. **138**:513-527 (April) 1941.

must be given before operation. The object of the present study is to determine whether this can safely be done.

Because of the possible serious consequences of operating on persons who have received this drug, patients on whom inguinal herniorrhaphy was to be performed were chosen. Since the operative procedure was limited to the abdominal wall, any postoperative hemorrhagic phenomena could be readily discovered and corrected. Twenty-three male patients were included in this series. Eighteen were operated on forty-eight hours after the administration of dicoumarin compound was begun orally; 5 were operated on at a still later date.

*Prothrombin and Clotting Times on the Morning of Operation of Patients Given Dicoumarin Compound*

Patient	Prothrombin Time (Seconds)	Clotting Time (Minutes)
1.....	24	15
2.....	38	12
3.....	180	8
4.....	23	8
5.....	66	11
6.....	35	15
7.....	37	14
8.....	17	18
9.....	49	30
10.....	16	13
11.....	18	20
12.....	20	10
13.....	23	21
14.....	45	16
15.....	72	18
16.....	30	12
17.....	16	11
18.....	35	12
19.....	35	8
20.....	21	10
21.....	44	22
22.....	29	12
23.....	19	9

Five grains (0.32 Gm.) of dicoumarin compound was given by mouth in the morning two days and one day before operation. In some instances 3 or 5 grains (0.19 or 0.32 Gm.) was given on the morning of operation. The table shows the values for prothrombin and clotting times the morning the patients were operated on. The Quick method for determining prothrombin time and the Lee-White method for ascertaining clotting time were used, normal values for the two methods being taken as sixteen to eighteen seconds and four to eight minutes, respectively.

In every instance the appearance of the incised tissues was normal. There was no unusual amount of oozing of blood or any difficulty with hemostasis. Twenty-one wounds healed primarily. Nothing abnormal was noted in the healing process. In the wounds of patients 2 and 19 hematomas developed which required aspiration. One aspiration of the hematoma was sufficient as the wounds subsequently healed completely.

This small series demonstrates that herniorrhaphy can be performed with reasonable safety on patients who have the impairment in clotting which dicoumarin compound produces. Apparently enough thromboplastin is liberated in the incised wound to promote reasonably satisfactory hemostasis after the wound is sutured. Experience has shown that dicoumarin compound should not be given to patients with ulcerating or granulating areas because of the danger of hemorrhage from these areas. Further studies are being made on the feasibility of performing other operations on patients who have received dicoumarin compound prior to operation. It is hoped that the tendency to increased coagulability of the blood associated with surgical procedures may be combated with safety even during the operation.

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# ASSOCIATION OF PERNICIOUS ANEMIA AND CARCINOMA OF THE STOMACH

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Before the introduction of liver therapy in 1926, the average duration of life after the onset of pernicious anemia was five years, and the majority of persons afflicted with the disease were dead after three years.<sup>1</sup> This short interval did not permit the development of many complications. At postmortem examination of subjects who had died of pernicious anemia, however, carcinoma of the stomach was frequently encountered.

In 1876 Quinke made the first mention of the association of pernicious anemia and carcinoma of the stomach in the same case.<sup>2</sup> Israel in 1890 and Roux in 1893 each reported a similar case.<sup>1b</sup> Before the turn of the century 3 more cases were reported by Lubarsch, and another was reported by Engle. The case reported by Waterfield<sup>3</sup> and Shackle in 1923 is perhaps the earliest example in the medical literature in which the association of the two conditions was confirmed at laparotomy; the lesion proved inoperable. The 11 cases reported by Conner and Birkeland in 1933 perhaps formed the first large series in which diagnosis of the two conditions had been made before death. In only 2 of these 11 cases did pernicious anemia precede carcinoma, and the authors expressed the opinion that in the majority of cases conclusions cannot be offered as to which condition is primary. In the same year Wilkinson

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From the Division of Medicine, the Mayo Clinic.

1. (a) McCann, W. S.: Pernicious Anemia, in Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1934, pp. 1016-1023. (b) Wilkinson, J. F.: Pernicious Anaemia and Malignant Disease, *Acta med. Scandinav.* 80:466-479, 1933.

2. Conner, H. M., and Birkeland, I. W.: Coexistence of Pernicious Anemia and Lesions of the Gastrointestinal Tract: I. Carcinoma of the Stomach; Consideration of Twenty Cases; Eleven Reported, *Ann. Int. Med.* 7:89-104 (July) 1933.

3. Waterfield, R. L.: Addison's Anaemia with Subacute Combined Degeneration of Spinal Cord Secondary to Cancer of the Stomach, *Guy's Hosp. Rep.* 73:208-210 (April) 1923.

collected 25 cases (including 1 of his own) of coexistence of the two diseases.<sup>4</sup> Since that time the medical literature has abounded in reports of cases. Eight cases were reported in 1935; 15, in 1936; 23, in 1937, and 16, in 1938. In 1936 Murphy and Howard,<sup>5</sup> in reviewing 440 cases of pernicious anemia, noted that carcinoma of the stomach was present in 4 cases (0.9 per cent). Apparently the assumption put forth by many of the early writers was right, namely, that with the prolongation of life expectancy resulting from the advent of liver therapy, an increased incidence of carcinoma of the stomach would be observed among patients with pernicious anemia.

TABLE 1.—*Reports of the Incidence of Carcinoma of the Stomach Associated with Pernicious Anemia\**

Dates	Pernicious Anemia (Cases)	Pernicious Anemia and Carcinoma (Cases)		Percentage	Reports of Cases: Authors
		Actual New Cases	Total Listed for Dates		
1917-1922	628	1†	1†	0.16	Conner and Birkeland <sup>2</sup>
1925-1927	...	4	..	....	Conner and Birkeland <sup>2</sup>
1928-1930	658	4	4	0.6	Conner and Birkeland <sup>2</sup>
1931-1932	...	2	..	....	Conner and Birkeland <sup>2</sup>
1932	...	1‡	..	....	Present series
1931-1933	...	3	..	....	Priestley, J. T., and Heck, F. J.: <i>Ann. Surg.</i> <b>101</b> : 839-843, 1935
1931-1934	906	11	16	1.76	Washburn and Rozendaal <sup>12</sup>
1935-1939	1,014	14	17§	1.7	Present series

\* Forty cases, 1917-1939, inclusive.

† Mentioned by Giffin and Bowler in 1923 but not reported in detail until Conner and Birkeland's series.

‡ Apparently not included in any previous series; hence reported in this paper as 1 of the 15 previously unreported cases but not included in the statistics since it does not fall within the 1935 to 1939 period.

§ Three of these cases were reported by Washburn and Rozendaal in 1938, but because they are part of the 1,014 cases of pernicious anemia observed during 1935 to 1939, they are included in the statistics of that period.

#### MATERIAL STUDIED

From 1917 to 1939, inclusive, 40 patients with both pernicious anemia and carcinoma of the stomach were examined at the Mayo Clinic; the cases of 25 of these have been reported previously. The incidence of carcinoma of the stomach among the patients of this group is given in table 1. In 26 of the 40 cases, the diagnosis of pernicious anemia preceded the diagnosis of gastric carcinoma; in only

4. Omitted were the following cases: 1 of Quincke (1876); 1 of Roux (1893); 1 of Davidsohn (1905); 1 of Giffin, H. Z., and Bowler, J. P.: *Minnesota Med.* **6**:13-16, 1923, included in Conner and Birkeland's series; 1 of Neuberger (1929); 1 of Duetsch-Eszenji (1928); 3 mentioned in Davidson and Gulland's book (1930); 1 of Henning (1930); 1 Saltzman (1931) (originally reported by Weinberg [1917] ?); 1 of Simpson (1931).

5. Murphy, W. P., and Howard, I.: *An Analysis of the Complications Occurring in a Series of Patients with Pernicious Anemia*, *Rev. Gastroenterol.* **3**:98-110 (June) 1936.

2 cases did the diagnosis of carcinoma precede the diagnosis of pernicious anemia, and in 12 cases the onset of the two diseases appeared to be simultaneous.

Although the number of patients with pernicious anemia seen at the clinic each year has increased only gradually, the number of cases in which pernicious anemia is associated with carcinoma of the stomach has increased markedly. For many years at the clinic, annual routine roentgen gastric studies have been advised for all patients with pernicious anemia on the assumption that an increasing number of carcinomas of the stomach would be disclosed. That this measure has been justified is evidenced by the fact that in 9 such cases in 1939 carcinoma of the stomach was diagnosed.

During the five year period from 1935 to 1939, inclusive, approximately 1,014 patients with pernicious anemia were treated at the clinic. Of this number, 17 (1.7 per cent) had carcinoma of the stomach also. A study of these 17 cases forms the basis for this report. A summary of the findings in these cases is presented in table 2.

#### INCIDENCE

Apparently the incidence of carcinoma of the stomach among persons afflicted with pernicious anemia is increasing, but whether the increase has any relation to the pathologic processes concerned in pernicious anemia or is due merely to the fact that today more patients with pernicious anemia are living longer into the cancer age as the result of liver therapy than patients of this type did formerly is impossible to say at present. Some authors have stated that the patient with pernicious anemia is slightly, although definitely, more likely to have carcinoma of the stomach than the normal person.<sup>6</sup> Proof of this belief, however, is difficult to establish. It is doubtful that the incidence of carcinoma of the stomach among those patients with pernicious anemia herein considered is representative of the incidence of carcinoma of the stomach. It is almost impossible to say whether the incidence of gastric carcinoma in association with pernicious anemia is greater or less than the incidence of carcinoma of the stomach alone in the same age group in the general population since the latter incidence cannot be determined. Pernicious anemia rarely develops before the age of 30.<sup>7</sup>

In 1938, in the United States, 23,666 white persons more than 40 years of age died of carcinoma of the stomach and the duodenum. This number represents a rate of death due to carcinoma of the stomach and the duodenum among white persons more than 40 years of age of

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6. Silverman, S.: Pernicious Anemia Followed by Carcinoma of the Stomach, *Lancet* 2:71-74 (July 11) 1936.

7. Castle, W. B., and Minot, G. R.: Pathological Physiology and Clinical Description of the Anemias, in Christian, H. A., and Mackenzie, J.: *Oxford Medicine*, New York, Oxford University Press, 1920, vol. 2, pt. 3, chap. 16, pp. 589-680.

0.57 per thousand.<sup>8</sup> It constitutes, moreover, 2.55 per cent of all deaths and 18.03 per cent of all deaths from carcinoma among the white population of this age group. If it is arbitrarily assumed that in the average

TABLE 2—Summary of Data in Seventeen Cases of Pernicious Anemia Associated with Carcinoma of the Stomach \*

Case	Sex	Pernicious Anemia		Interval Between Dis- eases (Yr)	Age of Onset (Yr)†	Carcinoma of the Stomach			Result
		Age of Onset (Yr)‡	Röntgenogram §			Situation	Treatment	Grade	
1§	M	59	Normal	0	59	Middle third	Partial gastrectomy	3	Died; aged 62 yr.
2	F	57	. .	0	57	Lower third	None	..	Patient refused operation
3	F	52	....	2	54	Lower third	Local resection	2	Died, aged 57 yr.
4	M	74	Normal	3	77	Upper half	None	.	Carcinoma inoperable
5§	M	65	Normal	5	70	Upper two thirds	Exploratory laparotomy	..	Died, aged 70 yr.
6	M	57	Normal	6	63	Middle third	Partial gastrectomy	4	Died, aged 64 yr.
7	F	52	Normal	8	60	Lower third	Partial gastrectomy	2	Well; aged 63 yr. (April 1940)
8	M	54	Normal	9	63	Middle third	Exploratory laparotomy	4	Died; aged 63 yr.
9	M	45	Normal	10	55	Lower third	None	2	Carcinoma discovered at necropsy
10	M	50	Normal	12	62	Lower third	Exploratory laparotomy	3	
11	F	46	. .	12	58	Lower third	Exploratory laparotomy	..	Died, aged 59 yr
12	M	45	. . .	12	57	Lower third	Partial gastrectomy	3	Well, aged 58 yr (October 1940)
13	M	55	. . .	12	67	Lower third	Partial gastrectomy	1	Well; aged 63 yr. (October 1940)
14	F	62	Normal	13	75	Middle third	Local resection	2	Died; aged 78 yr
15	M	54	. . . .	14	68	Entire	Exploratory laparotomy		
16	M	58		15	73	Upper third	None	.	Carcinoma inoperable patient died; aged 74 yr
17	M	42	. . . .	15	57	Entire	None	..	Carcinoma inoperable

\* 1935-1939, inclusive

† As nearly as could be judged from signs and symptoms

‡ At or near the time the diagnosis of pernicious anemia was made

§ Reported by Washburn and Rozendaal in 1938

8. Deaths from Each Cause. Tabulation by Age, Race and Sex; United States, 1938, in Vital Statistics—Special Reports, United States Department of the Interior, Bureau of the Census, June 20, 1940, vol 9, no 51, pp. 621-667.

Estimated population = 130,000,000

White persons more than 40 years of age (Metropolitan Life Insurance Co) = 41,665,000

White persons more than 40 years of age who died of carcinoma of the stomach and the duodenum = 23,666

$\frac{23,666}{41,665,000} = 0.057$  per cent



case gastric carcinoma exists for five years before it causes death, the incidence of carcinoma of the stomach in the particular group in question becomes 2.85 per thousand. Even if ten years is taken to be the average duration of the disease (and certainly the duration of gastric symptoms is not an indication of the duration of the pathologic process), the incidence is less than 6 per thousand. Among the patients with pernicious anemia visiting the clinic the incidence of 17 per thousand would be higher than one might expect if the patients with pernicious anemia in this group were comparable with the general white population more than 40 years of age.

In the five years from 1935 to 1939, inclusive, gastric resection for malignant disease was performed at the clinic in 575 cases. In 17 of the cases the lesion was sarcoma; in 14 cases resection was total. These 575 resections represent approximately half of the operations performed in that period for malignant disease of the stomach. Although different writers have reported the development of pernicious anemia following gastric carcinoma and also following resection of the stomach for carcinoma, in not 1 case in this series did pernicious anemia develop after gastric resection. Of the 17 cases included in table 2, pernicious anemia was present before operation in 4 (cases 6, 7, 12 and 13) in which partial gastrectomy was performed. Ivy, Morgan and Farrell<sup>9</sup> performed total gastrectomy on 14 dogs, none of which subsequently had pernicious anemia. These data, of course, raise the question of whether there is not some other part of the body besides the "pyloric organ" which supplies the "intrinsic factor."<sup>10</sup> Hurst reported 4 cases in which pernicious anemia developed after total gastric resection.<sup>11</sup> In 1933, Wilkinson was able to collect from the literature reports of 12 cases in which pernicious anemia developed after gastric resection for malignant disease.

#### AGE OF ONSET

Because carcinoma of the stomach may occur and even be far advanced without producing any symptoms other than those of mild, vague indigestion, it is difficult to state in all cases just when the onset of symptoms referable to carcinoma occurred. It was felt, however, that in all but 2 of the 17 cases presented in table 2, pernicious anemia

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9. Ivy, A. C.; Morgan, J. E., and Farrell, J. I.: The Effects of Total Gastrectomy: Experimental Achylia Gastrica in Dogs with the Occurrence of a Spontaneous Anaemia and Anaemia of Pregnancy, *Surg., Gynec. & Obst.* **53**:611-620 (Nov.) 1931.

10. Meulengracht, E.: Histologic Investigations into the Pyloric Gland Organ in Pernicious Anemia, *Am. J. M. Sc.* **197**:201-214 (Feb.) 1939.

11. Hurst, A. F.: Achlorhydria and Achylia Gastrica, and Their Connection with Addison's Anaemia-Subacute Combined Degeneration Syndrome and Simple (Non-Addisonian) Achlorhydric Anaemia, *Quart. J. Med.* **1**:157-177 (Jan.) 1932.

definitely preceded the onset of carcinoma by two to fifteen years. In each of these 2 cases both diseases were present when the patient first presented himself for examination, and it was impossible to say definitely which, if either, disease was primary. Although many authors have reported the development of pernicious anemia both before and after the diagnosis of gastric carcinoma, by far the majority of those reporting the coexistence of the two conditions have stated that pernicious anemia was the primary disease.<sup>12</sup> In this study the average age at onset of symptoms of pernicious anemia was 54.5 years, whereas that for the onset of symptoms thought due to carcinoma was 63.2 years. The average interval between the two diseases was eight and seven-tenths years, an interval much greater than the average survival period of patients with pernicious anemia in the days before liver therapy. The increased period of survival probably accounts in part for the present increasing frequency of gastric carcinoma in association with pernicious anemia.

#### ACHLORHYDRIA

Achlorhydria is an invariable finding in cases of pernicious anemia and is present in the majority of cases of gastric carcinoma.<sup>13</sup> All of the 17 patients in this study had achlorhydria. In 10 of the cases it was demonstrated three to twenty-four years before the discovery of carcinoma. In case 8 (table 2), achlorhydria was detected fifteen years before the onset of pernicious anemia and twenty-four years before the discovery of carcinoma of the stomach, when the patient had attained the age of 63 years. Numerous authors have described cases in which achlorhydria preceded the onset of pernicious anemia.<sup>14</sup> Nearly all authorities are agreed that although atrophy of the gastric mucosa is supposed to improve under treatment, the achylia of pernicious anemia persists even after years of intensive therapy and after evidence of apparent control of the condition has been manifested.<sup>15</sup> Such improvement in the gastric mucosa was recently disputed; Hurst and others reported a case in which free hydrochloric acid did return. Such instances are definitely rare, however, and under the circumstances<sup>14a</sup> one would dispute the diagnosis of pernicious anemia.

12. Washburn, R. W., and Rozendaal, H. M.: Gastric Lesions Associated with Pernicious Anemia, *Ann. Int. Med.* **11**:2172-2180 (June) 1938.

13. (a) Rozendaal, H. M., and Washburn, R. N.: Gastric Secretion in Cases of Pernicious Anemia, *Ann. Int. Med.* **11**:1834-1837 (April) 1938. (b) Conner and Birkeland.<sup>2</sup> (c) Murphy and Howard.<sup>5</sup> (d) Minot.<sup>7</sup>

14. (a) Johansen, A. H.: Achylia in Pernicious Anemia After Liver Treatment: Examinations After Histamine Injections, *J. A. M. A.* **92**:1728-1730 (May 25) 1929. (b) Rozendaal and Washburn.<sup>13a</sup> (c) Ivy, Morgan and Farrell.<sup>9</sup>

15. (a) Carey, J. B.: Gastrosopic Observations in a Pernicious Anemia, *Minnesota Med.* **23**:311-313 (May) 1940. (b) Miller, T. G.: The Relation of Gastritis to the Anemias, *Internat. Clin.* **1**:173-178, 1940. Johansen.<sup>14a</sup>

## TREATMENT

Of the 17 cases of associated pernicious anemia and carcinoma of the stomach which form the basis of this report, operation on the stomach was performed in 12. In 5 of these cases the growth was found to be inoperable. In 3 of the 5 cases in which operation was not performed, the carcinoma was judged inoperable on the basis of roentgen examination; in 1 case the patient refused operation, and in 1 case the carcinoma was discovered at necropsy, although results of a roentgen examination of the stomach made a short time before death had revealed no lesion. Of the 7 cases in which surgical treatment was carried out, local excision of polypoid growths was done in 2, and partial gastrectomy was done in the other 5 (table 2).

## PATHOLOGIC NATURE

In most cases gastric carcinoma occurs in the pyloric region.<sup>16</sup> Hurst expressed the belief that gastric carcinoma of this type is the indirect result of friction at the pyloric portion.<sup>16</sup> In our study the carcinoma was located in the lower third of the stomach in 8 cases (47 per cent); it was situated in the middle third in 4 (23.5 per cent); in the upper portion in 3 (17.6 per cent), and in 2 cases (11.7 per cent) the whole stomach was involved.

Microscopic studies were made of the material obtained in the 7 cases in which surgical treatment was given; biopsy was done in 2 of the cases in which the lesion was inoperable and in the case in which carcinoma was discovered at necropsy. All the lesions proved to be adenocarcinoma. In these 10 cases the degree of malignancy according to Broders' classification on the basis of 1 to 4 (in which 1 indicates the mildest, and 4, the most severe condition) was as follows: in 1 case, grade 1; in 4 cases, grade 2; in 3 cases, grade 3, and in 2 cases, grade 4.

## POLYPS

Among the 1,014 patients with pernicious anemia observed from 1935 to 1939, inclusive, there were 4 patients with gastric polyps (considered benign)—an incidence of 0.39 per cent. In 2 of the 4 cases, the diagnosis was made by roentgen examination only; in 1 case the polyp was removed by local excision, and in 1 case multiple polyposis of the stomach necessitated resection of half of the stomach. At necropsy on subjects who died from pernicious anemia Brown<sup>17</sup> observed benign

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16. Hurst, A. F.: Precursors of Carcinoma of the Stomach, *Lancet* 2:1023-1028 (Nov. 16) 1929.

17. Brown, M. R.: The Pathology of the Gastro-Intestinal Tract in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord (A Study of One Hundred and Fifty-One Autopsies), *New England J. Med.* 210:473-477 (March 1) 1934.

gastric tumors in 8 per cent of the cases and in a large series of general postmortem examinations reported an incidence of 0.003 per cent.

#### COMMENT

The exact relation, if any, of pernicious anemia and gastric carcinoma is unknown; indeed, the causation of either condition is not fully understood. There are workers who hold that there is no relation between the two diseases and that the co-existence of the two conditions is purely coincidental.<sup>18</sup> In 1931 Strandell<sup>19</sup> wrote:

. . . Present material lends no support to the view that some causal connection would exist between pernicious anemia and carcinoma of the stomach. Yet they hit the same individual often. The future alone will show whether Saltzman's theory of a common basis for the two conditions is correct.

The burden of proof seems to lie on those who would disprove this theory. The purpose of our study was to test this hypothesis.

Indicating a possible relation between pernicious anemia and carcinoma of the stomach is the fact that both diseases occur most frequently among persons more than 40 years of age, although the average age of patients with pernicious anemia is slightly less than that of patients with gastric carcinoma.<sup>7</sup>

Achlorhydria also is common to both conditions, but it should be regarded as a symptom rather than as a clinical entity. Its occurrence, as compared with that of either pernicious anemia or carcinoma of the stomach, is far too common to be regarded as the direct cause of either condition.<sup>1b</sup> Faber<sup>20</sup> reported that about 40 per cent of persons more than 60 years of age have anacidity. Obviously neither gastric carcinoma nor pernicious anemia develops this frequently. During the period from 1921 to 1929, inclusive, although approximately 15 per cent of the population had achlorhydria, only 43 persons in 100,000 had pernicious anemia.<sup>20</sup> Thus the chance that persons with achlorhydria would have pernicious anemia also was about 3 in 1,000. The incidence of pernicious anemia is probably no greater now. Administration of dilute hydrochloric acid by mouth has no effect of itself on pernicious anemia, and carcinoma frequently develops in a stomach the acid secretion of which is perfectly normal or even increased. Although achlorhydria is

18. Held, I. W., and Goldbloom, A. A.: Carcinoma of the Stomach in a Cured Case of Addison-Biermer's (Pernicious) Anemia, *J. A. M. A.* **108**:1398-1400 (April 24) 1937. Goldhamer, S. M.; Bethell, F. H.; Isaacs, R., and Sturgis, C. C.: Blood: A Review of the Recent Literature, *Arch. Int. Med.* **59**:1051-1111 (June) 1937.

19. Strandell, B.: Pernicious Anemia: A Study of One Hundred and Seventeen Cases, *Acta med. Scandinav.*, 1931, supp. 40, pp. 1-124.

20. Faber, K.: Gastritis and Its Consequences, New York, Oxford University Press, 1935.

usually thought indicative of previous gastritis, in not every instance is achlorhydria the result of gastritis.<sup>20</sup> Hurst wrote of an inborn error of secretion not accompanied by structural changes.<sup>21</sup> Three other accepted causes of achlorhydria are: functional (psychic) disturbances; the presence of toxins which produce achlorhydria without gastric changes, such as the achlorhydria associated with exophthalmic goiter, and deficiency disease, such as beriberi and pellagra.<sup>20</sup> Such anacidity is often transient. Bloomfield and Polland<sup>22</sup> mentioned an "unexplained anacidity." Disposition to anacidity was thought by Faber to be due to an inferior power of resistance to injurious influences.

Chronic gastritis, especially the atrophic form, or gastric atrophy, is frequently associated with both pernicious anemia and gastric carcinoma, although its presence is not essential to the development of either. Neither the cause nor the consequences of chronic gastritis are fully understood. Many writers have expressed the belief that carcinoma of the stomach developing in association with pernicious anemia is frequently secondary to the gastric changes, causal or resultant, which accompany pernicious anemia. Although the atrophic form of chronic gastritis, or gastric atrophy, is a frequent finding in the presence of pernicious anemia, not all investigators will agree that it is an invariable finding.<sup>23</sup> Magnus and Ungley<sup>24</sup> described a "characteristic lesion localized to the region of the 'body mucosa' and not affecting the pyloro-duodenal region" and expressed the opinion that histologically the lesion was "not the end result of inflammation." Meulengracht reported identical findings, and although he expressed the belief that the intrinsic factor is secreted by the pyloric glands and the histologically identical Brunner's glands of the duodenum, he suggested the possibility of a pacemaker hormone secreted by the fundus which acts on the pyloric organ. Absence or improper action of this fundic hormone would then result in lessened or absent secretion of the intrinsic factor and resultant pernicious anemia. Many investigators have demonstrated the frequency with which chronic gastritis accompanies gastric carcinoma; some have said that it is a constant finding.<sup>25</sup> Gastritis of this type, most writers have stated, is the precursor of carcinoma and prepares the soil for the development of the lesion.<sup>26</sup> Achlorhydria in these cases has been judged

21. Faber.<sup>20</sup> Hurst.<sup>11</sup>

22. Bloomfield, A. L., and Polland, W. S.: The Fate of People with Unexplained Gastric Anacidity: Follow Up Studies, *J. Clin. Investigation* **14**:321-324 (May) 1935.

23. McCann.<sup>1a</sup> Brown.<sup>17</sup>

24. Magnus, H. A., and Ungley, C. C.: The Gastric Lesion in Pernicious Anemia, *Lancet* **1**:420-421 (Feb. 19) 1938.

25. Konjetzny, G. E., cited by Hurst.<sup>11</sup> Brown.<sup>17</sup> Magnus and Ungley.<sup>24</sup>

26. (a) Judd, E. S., Jr.: Possible Relationship of Residual Lesions of Ulcerative Gastritis to the Development of Carcinoma of the Stomach, *Proc. Staff Meet., Mayo Clin.* **14**:52-56 (Jan. 25) 1939. (b) Miller.<sup>15b</sup> (c) Brown.<sup>17</sup> (d) Faber.<sup>20</sup>

by many observers to be the result of chronic gastritis or degenerative atrophic changes which are present before malignant degeneration takes place in the gastric mucosa.<sup>27</sup> It is an old dictum that carcinoma never develops in a healthy stomach.<sup>16</sup> There is evidence that the entire mucosa is host to the malignant disease and that the change is a gradual diffuse transformation.<sup>26a</sup> However, most authors have agreed that chronic gastritis alone is not the only factor, other important factors being predisposition and proper age. Otherwise, physicians would see many more patients with gastric carcinoma than at present, especially with gastric carcinoma in association with pernicious anemia or with chronic atrophic changes in the gastric mucous membrane from whatever cause.<sup>28</sup>

#### SUMMARY

Reference is made to 15 cases of associated pernicious anemia and carcinoma of the stomach in addition to 25 similar cases previously reported from the Mayo Clinic.

During the five year period from 1935 to 1939, inclusive, approximately 1,014 patients with pernicious anemia were seen at the clinic. Seventeen of these patients had carcinoma of the stomach also—an incidence of approximately 1.7 per cent. The findings in these cases are summarized in table 2. This incidence seems slightly greater than the calculated incidence of gastric carcinoma among the adult general population. Carcinoma in these cases was similar in situation and grade of malignancy to carcinoma of the stomach in cases in which it is not complicated by pernicious anemia. The average age at which the onset of symptoms referable to pernicious anemia occurred was 54.5 years while that at which the symptoms of carcinoma of the stomach appeared was 63.2 years. The relation of the two diseases is discussed briefly, and although present evidence is insufficient to prove a direct relation between the two diseases, there are grounds for suspecting that persons with pernicious anemia are slightly more likely than normal persons to have gastric carcinoma.

The Mayo Clinic.

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27. (a) Hurst, A. F.: Cancer of the Alimentary Tract: Its Pathogenesis and Its Prophylaxis, *Lancet* 1:553-558 (March 11) 1939. (b) Hurst.<sup>16</sup> (c) Faber.<sup>20</sup>

28. Faber.<sup>20</sup> Judd.<sup>26a</sup> Hurst.<sup>27a</sup>

# PERITONEAL FLUID AND GASTRIC CONTENTS IN CASES OF PERFORATED PEPTIC ULCER

CHARLES M. HENRY, M.D.

DETROIT

Few real surgical emergencies remain, but perforation of a peptic ulcer must be classed as one of the conditions demanding immediate surgical therapy. Much has been written on this subject, but there would seem to be a place for a more fundamental approach toward the bacteriologic and chemical problems involved. Perusal of the literature reveals a predominance of papers dealing with statistics or with points of technic rather than planned studies. It is the purpose of this paper to present data obtained from observations on a number of patients with benign ulcers of the stomach or the duodenum with free perforation into the general peritoneal cavity. I exclude from this group all malignant ulcers with perforation or posterior benign ulcers which have perforated into the lesser peritoneal cavity.

There is fairly general agreement <sup>1</sup> that intra-abdominal infection is a major cause of death in cases of gastric and duodenal perforations, whether operation was done or not. This is borne out by a series of 179 persons who have had simple repair of perforated ulcers at the City of Detroit Receiving Hospital within the three year period between June 1938 and January 1942. Of these, 24 (13.4 per cent) died; 16 were examined at autopsy. In 13 of the 16 either generalized peritonitis or intra-abdominal abscesses were revealed as the major cause of death. In none of these was there evidence of postoperative leak at the ulcer site. All of these patients had either simple application of a tab of omentum over the perforation <sup>2</sup> or infolding of the involved portion by sutures plus application of a tab of omentum. The small transverse incision described by Amendola <sup>3</sup> and Hartzell and Sorock <sup>4</sup> was used routinely. No intraperitoneal drains were used.

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This study was aided by a grant from the Theodore A. McGraw Fund.

From the Department of Surgery, Wayne University College of Medicine, and the City of Detroit Receiving Hospital.

1. DeBakey, M.: *Acute Perforated Gastroduodenal Ulceration*, Surgery **8**:852, 1940.

2. Graham, R. R.: *The Treatment of Perforated Duodenal Ulcers*, Surg., Gynec. & Obst. **64**:235, 1937.

3. Amendola, F. H.: *Simplified Approach for Suture of Acute Perforation of Peptic Ulcer*, Surg., Gynec. & Obst. **64**:76, 1937.

4. Hartzell, J. B., and Sorock, M. L.: *Surg., Gynec. & Obst.* **69**:669, 1939.

It has been customarily assumed that chemical peritonitis occurs during the early hours following perforation with bacterial invasion later. Thus Hurst and Stewart,<sup>5</sup> in their monograph on peptic ulcer, stated: . . . Peritonitis is non-infective and is caused by the irritant action of acid chyme. At the end of 12 hours the peritoneal cavity is invaded by bacteria which convert the simple irritative peritonitis into a virulent septic form.

Davison, Aries and Pilot<sup>6</sup> have offered the suggestion that

. . . the presence of an early "chemical peritonitis" causes a cessation of peristalsis with a concomitant cessation of secretion of hydrochloric acid, thus allowing for a proximal migration of bacteria from the lower bowel.

I believe that such concepts do not represent the true state of affairs.

#### METHOD

All cases reported here were personally studied. In those cases in which operation was performed by other members of the staff, I collected the specimens at the time of operation and followed the patient thereafter.

The fluid was collected in a Luer syringe through a fenestrated rubber tube. This permitted collection without interference from omentum and with little contact with air. Determinations of hydrogen ion concentration were done by means of the glass electrode (Beckman  $p_H$  meter) at room temperature, and the chloride determinations were carried out by the method of Wilson and Ball. Bacteriologic cultures were made from swabs taken directly from the peritoneal cavity and from a portion of the sample removed by syringe. Meat broth and heart infusion agar were the mediums used. Samples for hydrogen ion concentration of the gastric contents were obtained postoperatively by aspirating fluid through Levine tubes which were used for decompression.

#### BACTERIOLOGIC STUDIES

There are relatively few reports on bacteriologic studies of the peritoneal exudate. Brenner,<sup>7</sup> Alexander<sup>8</sup> and Ulrich<sup>9</sup> were unable to obtain bacterial growth from peritoneal fluid cultured as late as twelve to eighteen hours after perforation of peptic ulcers. Brütt<sup>10</sup> and

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5. Hurst, A. F., and Stewart, M. J.: *Gastric and Duodenal Ulcer*, New York, Oxford University Press, 1939.

6. Davison, M.; Aries, L. D., and Pilot, I.: *A Bacteriologic Study of the Peritoneal Fluid in Perforated Peptic Ulcer*, Surg., Gynec. & Obst. **68**:1017, 1939.

7. Brenner, E. C.: *Perforated Ulcers of the Duodenum: Study of Forty-One Cases*, Ann. Surg. **102**:185, 1935.

8. Alexander, E. G.: *Acute Perforation of Gastric and Duodenal Ulcers with a Report of Thirty-Six Cases*, Ann. Surg. **66**:72, 1917.

9. Ulrich, P.: *De la gastro-pyloréctomie et de la duodéno-pyloréctomie immédiates dans la traitement des ulcères perforés de l'estomac et du duodénum*, Rev. de chir., Paris **41**:467, 1931.

10. Brütt, H.: *Bacteriologische Gesichtspunkte zur Frage der Resektion des perforierten Magen-Duodenalgeschwürs*, Beitr. z. klin. Chir. **138**:601, 1926.



Judine<sup>11</sup> found a high incidence of positive cultures in fluid from perforations less than twelve hours old. My observations (table 1) indicate that there is almost as high a percentage of positive bacteriologic cultures in perforations under six hours old as there is in those of longer duration.

It occurred to me that some of the negative cultures might be due to dilution of organisms. To aid in eliminating this factor both a swab and a larger specimen, usually 3 cc., were taken in each of a series of 48 cases and incubated in broth. The results are tabulated in table 2.

TABLE 1.—*Bacterial Growth in Peritoneal Fluid from Perforations Under and Over Six Hours Old*

	Growth	No Growth	Percentage of Growth
Swab cultures from perforations under 6 hr. old.....	38	23	62
Swab cultures from perforations over 6 hr. old.....	27	14	66

TABLE 2.—*Bacterial Growth from Both Swab and Larger Specimens of Peritoneal Fluid*

	Total Cases	Growth	No Growth	Percentage of Growth
Swab.....	48*	31	17	65
3 cc. ....	48*	39	9	81

\* Same cases.

TABLE 3.—*Incidence of Organisms in Sixty-Five Cultures of Peritoneal Fluid*

Nonhemolytic streptococci (including <i>Str. viridans</i> ).....	55
Hemolytic streptococci.....	1
Staphylococci.....	6
<i>Bacillus coli</i> .....	6
Miscellaneous.....	4

A fairly definite increase in the incidence of positive cultures may be noted with the larger specimens as compared with the swab specimens.

The organisms recovered in 65 cases in which there were positive cultures are listed in table 3. The high incidence of the nonhemolytic streptococci is probably related to the predominance of this organism in the oral cavity.

Quantitative estimation of bacterial growth from the peritoneal fluid was made by mixing 3 cc. of fluid with melted agar medium in Petri

11. Judine, S.: Nouvelle série d'ulcères perforés de l'estomac et du duodénum, J. de chir. 38:159, 1931.

dishes. The colonies were counted after proper incubation. This rough quantitating was done in an attempt to correlate volume of intraperitoneal fluid and concentration of organisms with the morbidity and mortality rates. The results obtained in 25 such cases are tabulated in table 4. No definite conclusions can be drawn from this short series.

TABLE 4.—*Quantitative Estimation of Bacteria in Peritoneal Fluid*

Patient	Duration of Perforation, Hr.	Type of Organism	Volume of Peritoneal Fluid, Cc.	Colonies per Cc.	Postoperative Course
G. S.	4	Str. viridans	250	70	Wound infection
J. McG.	11	Str. viridans	700	15	Died of multiple abdominal abscesses
C. M.	3	Anhemolytic streptococcus	100	4	Uneventful
R. W.	3½	Staph. albus	50	3	Died of pneumonia
F. B.	4	No growth	150	No growth	Uneventful
M. P.	10	No growth	150	No growth	Uneventful
G. L.	2	No growth	20	No growth	Uneventful
K. McC.	11	Str. viridans	1,000	15	Uneventful
A. A.	5½	Anhemolytic streptococcus; Str. viridans	60	5	Died of empyema and abdominal abscess
P. H.	5	Anhemolytic streptococcus; B. coli	100	Innumerable	Uneventful
G. N.	7	Anhemolytic streptococcus	100	13	Died of hemolytic streptococic septicemia
G. W.	11	Str. viridans	20	7	Uneventful
J. G.	4	Str. viridans; anhemolytic streptococcus	?	125	Pelvic abscess
L. P.	5½	Anhemolytic streptococcus	30	200	Uneventful
J. E.	11	Yeasts	500	70	Uneventful
A. S.	9	Anhemolytic streptococcus; Staph. albus	20	56	Uneventful
J. T.	4	Anhemolytic streptococcus; B. lactis aerogenes	10	52	Uneventful
J. R.	4	Yeasts	50	Innumerable	Uneventful
C. C.	11	Str. viridans; B. coli	500	40	Died of intraperitoneal abscesses
M. C.	8	Str. viridans; B. coli	120	Innumerable	Uneventful
A. M.	4	Str. viridans	300	83	Pelvic abscess
W. C.	9	No growth on broth	500	9 (type not determined)	Died; cause not determined; no autopsy
G. G.	4½	Str. viridans	300	Innumerable	Wound abscess
F. S.	4	B. coli; anhemolytic streptococcus	90	100	Died of pneumonia; no autopsy
W. M.	7	Anhemolytic streptococcus; Staph. aureus	?	57	Uneventful

## CHEMICAL STUDIES

It has been stated that normal gastric juice has a bacteriostatic effect on micro-organisms.<sup>12</sup> Broth cultures of intragastric contents from our patients were almost always productive of bacterial growth. In a large number of persons with perforations, the hydrogen ion concentration of gastric juice was found to be low at the time of operation. This was true even of the perforations of briefest duration. Chart 1 illustrates

12. Arnold, L.: The Bacterial Flora Within the Stomach and Small Intestine, Am. J. M. Sc. 186:471, 1933.

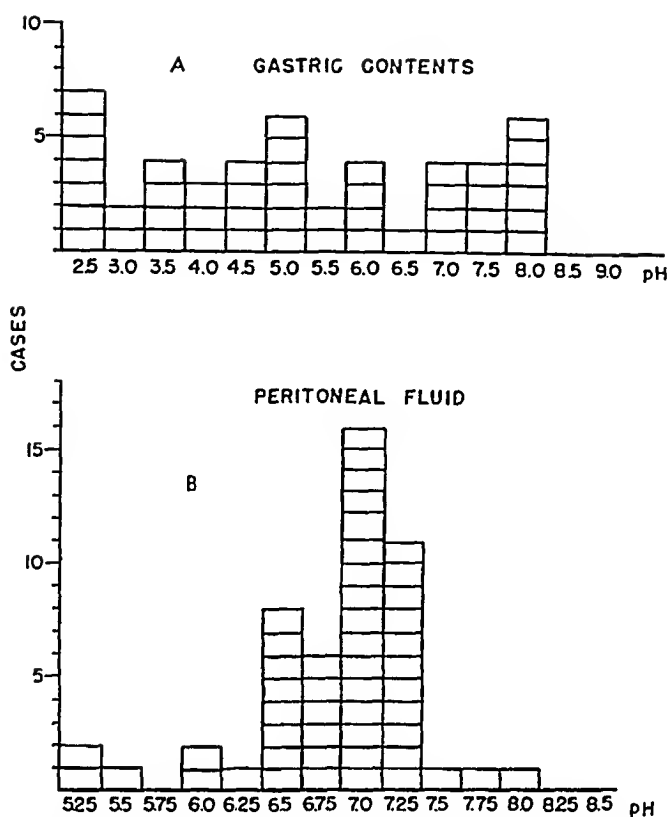


Chart 1.—Range of  $p_H$  determinations (*A*) of gastric contents aspirated before closure of perforated gastric and duodenal ulcers and (*B*) of peritoneal fluid removed at operation. Each rectangle represents 1 case.

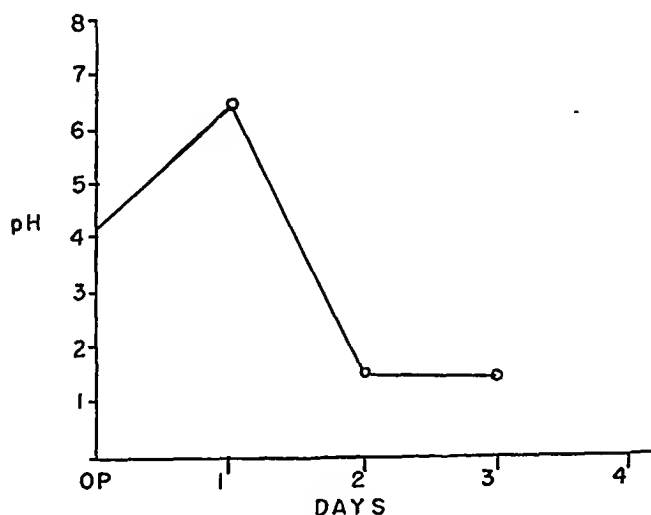


Chart 2.—Change in gastric  $p_H$  following closure of perforated ulcer (patient W. T.). *OP*, operation.

these findings graphically. Interesting but unexplained was the wide range of  $p_H$  values with no relation to how long the perforation had been present.

Finding the gastric acidity low at the time of operation I was interested in knowing how soon normal hydrogen ion concentration would be reached. This was found to occur twenty-four to forty-eight hours postoperatively. Chart 2 illustrates graphically a typical case. Generally a rapid return to normal acidity, e. g.,  $p_H$  1.5 to  $p_H$  0.2, was a favorable prognostic sign.

Of particular interest was the nature of the fluid within the abdominal cavity at the time of operation. One might expect to find a wide range of acidity dependent on the time consumed by the operation, the size of the opening and the acidity of the gastric juice. Surprisingly, practically all the fluids examined were neutral. Chart 1 shows that most of the  $p_H$  determinations ranged between 6.50 to 7.25. Furthermore, the chloride concentration of each specimen was that of blood plasma, approximately 100 milliequivalents per liter. This was constant regardless of the acidity of the gastric juice, the duration of the perforation or the volume of fluid in the peritoneal cavity.

#### COMMENT

It has often been maintained that the morbidity and mortality rates associated with perforated ulcers are in direct ratio to the duration of perforation. This is not strictly true. In my own series, 11 of 20 deaths occurred in patients operated on within ten hours of the onset of perforation. Bergh, Bowers and Wangenstein<sup>13</sup> listed the factors which they considered important in governing the mortality rate following perforation of a viscus; in short these relate to: (1) the number and the virulence of escaping organisms; (2) the resistance of the host. This classification, which was based on animal experiments, appears generally to cover the problem in human beings. Certainly a person with a perforation must be estimated in terms of all the factors rather than on a basis of time alone.

From my observation I believe it is questionable whether chemical peritonitis is of much significance. It is more probable that micro-organisms are of importance from the onset of perforation. Hydrochloric acid must disappear from the gastric juice rapidly after perforation, if indeed it is not absent at the moment of perforation. Blalock<sup>14</sup> showed

13. Bergh, G. S.; Bowers, W. F., and Wangenstein, O. W.: Perforation of Gastrointestinal Tract: An Experimental Study of Factors Influencing Development of Peritonitis, *Surgery* 2:196, 1937.

14. Blalock, A.: Experimental Studies on the Effects of the Perforation of Peptic Ulcer, *Surg., Gynec. & Obst.* 61:20, 1935.

that gastric juice injected intraperitoneally in dogs is not lethal. It is true that mixtures of bile and pancreatic juice were occasionally lethal to dogs in Blalock's experiments, but I have never observed gross bile in the peritoneal fluid resulting from a duodenal perforation. Blalock indicated that his animals suffered from shock. It is important to note that shock is not a part of the picture of rupture of a peptic ulcer. In none of my cases was shock evident except in those cases in which death from peritonitis occurred and then only terminally. From the chemical nature of the intra-abdominal fluid, the peritoneum must begin secretory activity immediately after perforation so as to maintain osmotic balance. There is no evidence which would indicate modification of the activity of bacterial growth either by the gastric contents or by the intra-abdominal fluid. Obviously, the fate of the bacteria or the host will be in part determined eventually by the cellular activity of the peritoneum.

#### SUMMARY

Bacterial infection of the peritoneal cavity is a major cause of death in cases of perforation in a peptic ulcer.

Micro-organisms are to be found in the peritoneal cavity soon after perforation of an ulcer.

The gastric acidity is low at the time of perforation, and bacteria are to be found in the gastric contents.

The peritoneal fluid obtained at operation on patients with perforation has a hydrogen ion concentration and a chloride content approaching that of blood plasma.

Dr. Charles G. Johnston, professor of surgery, Wayne University College of Medicine, gave much helpful criticism and advice in the preparation of this paper.

Wayne University College of Medicine.

# BEHAVIOR OF RABBITS AFTER INFECTION WITH TOXIGENIC AND NONTOXIGENIC STAPHYLOCOCCI

AN EXPERIMENTAL STUDY

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The full role of exotoxin in the pathogenesis of systemic staphylococcic infections has not yet been demonstrated.<sup>1</sup> The symptoms of systemic infections in human beings due to toxigenic staphylococci differ from the symptoms of those due to nontoxigenic staphylococci,<sup>2</sup> and this difference is sufficiently pronounced to make it possible to determine from clinical characteristics alone whether the symptoms are primarily due to the effect of staphylococcic exotoxin.<sup>2d</sup> Previous reports have described the clinical response of the rabbit<sup>3</sup> and more

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From the Laboratory Division, Hospital for Joint Diseases.

1. (a) Blair, J. E.: The Pathogenic Staphylococci, *Bact. Rev.* **3**:97 (June) 1939. (b) Flaum, A.: Studies in Staphylococci and Staphylococcal Immunity, *Acta path. et microbiol. Scandinav.*, 1938, supp. 35, p. 1. (c) Nélis, P.; Bouckaert, J. J., and Picard, E.: Contribution à l'étude de la toxine staphylococcique, *Ann. Inst. Pasteur* **52**:597 (June) 1934. (d) Valentine, F. C. O.: Further Observations on the Rôle of the Toxin in Staphylococcal Infection, *Lancet* **1**:526 (March 7) 1936.

2. (a) Baker, L. D.: Acute Osteomyelitis with Staphylococcus Septicemia: Clinical Report on Use of Chemotherapy and Staphylococcus Antitoxin in Its Treatment, *South. M. J.* **34**:619 (June) 1941. (b) Baker, L. D., and Shands, A. R., Jr.: Acute Osteomyelitis with Staphylococcemia: A Clinical Report on the Use of Antitoxin in Its Treatment, *J. A. M. A.* **113**:2119 (Dec. 9) 1939. (c) Joyner, A. L., and Smith, D. T.: Acute Staphylococcus Osteomyelitis: The Use of Staphylococcus Antitoxin as Aid to Management of Toxemia and Staphylococcemia, *Surg., Gynec. & Obst.* **63**:1 (July) 1936. (d) Kleiger, B., and Blair, J. E.: Correlation Between Clinical and Experimental Findings in Cases Showing Invasion of the Blood Stream by Staphylococci, *ibid.* **71**:770 (Dec.) 1940. (e) Stookey, P. F., and Scarpellino, L. A.: Staphylococcus Septicemia, *South. M. J.* **32**:173 (Feb.) 1939.

3. (a) Burnet, F. M.: The Exotoxins of Staphylococcus Pyogenes Aureus, *J. Path. & Bact.* **32**:717 (Oct.) 1929. (b) Dolman, C. E.: Pathogenic and Antigenic Properties of Staphylococcus Toxin, *Canad. Pub. Health J.* **23**:125 (March) 1932. (c) Kellaway, C. H.; Burnet, F. M., and Williams, F. E.: The Pharmacological Action of the Exotoxin of Staphylococcus Aureus, *J. Path. & Bact.* **33**:

(Footnote continued on next page)

specifically of the rabbit heart<sup>4</sup> to the intravenous injection of exotoxin. With these clinical and experimental reports as a point of departure, the purpose of the present work is to extend these observations by comparing the clinical and electrocardiographic responses in rabbits receiving intravenous injections of staphylococcus exotoxin and toxin-free suspensions of living toxigenic or nontoxigenic staphylococci.

#### METHODS

Rabbits averaging 2,300 Gm. in weight were used. Cardiac action was recorded with a standard clinical electrocardiographic apparatus.<sup>5</sup> All the electrocardiograms were taken in lead II. The right upper and left lower extremities were anointed with conducting jelly, and soft copper wire electrodes to be connected to the poles of the instrument were wrapped around them. Readings were taken before the injection and at intervals thereafter. Rectal temperatures were taken with an ordinary clinical mercury thermometer. The rabbits were under constant observation for twenty-four to thirty hours after injection and were frequently observed thereafter until death.

Two strains of pathogenic staphylococci were used in these experiments, one a toxigenic strain and the other nontoxigenic. The toxigenic strain (Wood 46) has been widely described in the literature. Our culture was received in September 1936 through the courtesy of Dr. H. J. Parish, of the Wellcome Physiological Research Laboratories, England. The nontoxigenic strain (no. 437) was isolated in this laboratory in October 1938 from the blood of a child with pyarthrosis of the knee. Both are strains of *Staphylococcus aureus*, and both give a positive coagulase reaction.<sup>6</sup> Blood agar is hemolyzed to some extent by both strains, but the Wood 46 produces a potent soluble alpha hemotoxin, while the no. 437 produces neither alpha nor beta hemotoxin.

Toxin was prepared with the Wood 46 strain by growing the organism in semi-solid Bacto brain-heart infusion agar in an atmosphere containing 30 per cent carbon dioxide for forty-eight hours at 37 C. The agar culture was filtered through gauze; the filtrate was centrifuged at high speed, and the supernatant material represented the toxin used in the experiments.

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889 (Oct.) 1930. (d) Rigdon, R. H.: Early Lesions Following Intravenous Administration of a Filterable *Staphylococcus* Toxin: A Study on the Dog and Rabbit, *Arch. Path.* **20**:201 (Aug.) 1935; *Staphylococcus* Toxin: A Résumé, *Am. J. M. Sc.* **199**:412 (March) 1940. (e) Weld, J. T. P., and Gunther, A.: Differentiation Between Certain Toxic Properties of Filtrates of Hemolytic *Staphylococcus Aureus*, *J. Exper. Med.* **54**:315 (Sept.) 1931.

4. (a) Dingle, J. H.; Hoff, E. H.; Nahum, L. H., and Carey, B. W., Jr.: The Effect of *Staphylococcus Aureus* Exotoxin on the Rabbit Heart, *J. Pharmacol. & Exper. Therap.* **61**:121 (Oct.) 1937. (b) Kraus, R., and Pribram, E.: Ueber *Staphylokokkentoxin* und dessen Antitoxin, *Wien. klin. Wchnschr.* **19**:493, 1906. (c) Russ, V. K.: Die Toxine und Antitoxine der pyogenen *Staphylokokken*, *Ztschr. f. exper. Path. u. Therap.* **18**:220, 1916. (d) Nélis, Bouckaert and Picard.<sup>1c</sup>

5. A standard clinical electrocardiographic apparatus was obtained through Mr. S. R. Hollander, of the General Electric X-Ray Corporation of New York.

6. Chapman, G. H.; Berens, C.; Peters, A., and Curcio, L.: Coagulase and Hemolysin Tests as Measures of the Pathogenicity of *Staphylococci*, *J. Bact.* **28**:343 (Oct.) 1934.

Washed cultures were prepared by suspending the growth from eighteen to twenty-four hour agar cultures in sterile physiologic solution of sodium chloride, centrifuging and washing three times in sterile solution of sodium chloride. Suspensions washed in this manner were shown to be free from any trace of exotoxin. The washed bacterial sediment was finally suspended in 5 cc. of sterile solution of sodium chloride. The infecting dose was 1 cc. of this suspension per kilogram of body weight.

## RESULTS

*Rabbits Receiving Staphylococcus Exotoxin.*—Seven rabbits were given single intravenous injections of staphylococcus exotoxin in doses varying from 0.031 to 1.0 cc. per kilogram of body weight. As a control, 1 rabbit received 0.5 cc. per kilogram of sterile culture medium processed in the same manner as the semisolid agar cultures. Only the rabbit which received the smallest dose of exotoxin and the control survived. The other rabbits died<sup>7</sup> in three to twenty-two minutes, except 1, which survived one hundred and sixty-seven minutes. The duration of survival tended to be inversely proportional to the amount of exotoxin injected.

The rabbits which died showed a characteristic pattern of changes in the heart rate. Before injection the rate averaged 254 beats per minute. Shortly after injection it diminished in each animal from 50 to 100 beats and then rose rapidly to a level 50 to 100 beats per minute above the original normal rate. From this height there was a sudden drop in the rate which was associated with rhythmic irregularities and electrocardiographic changes indicative of myocardial damage. Among these were heart block, ventricular tachycardia, fibrillation and nodal beats, as well as distortion of the individual components of the curve (fig. 1).

Clinically the rabbits appeared normal for a short time after injection. They then became restless and apprehensive; this was followed by unsteadiness, paralysis of the hinglegs and irregular and gasping respirations. Incoordinate running movements were accompanied by violent convulsions with opisthotonos and retraction of the neck and just before death by involuntary expulsion of urine and feces. The temperature taken immediately after death did not differ significantly from that taken just before the injection of toxin.

*Rabbits Receiving Washed Toxigenic Staphylococci.*—One cubic centimeter per kilogram of body weight of a washed culture of the toxigenic strain of staphylococcus was injected intravenously into 3 rabbits. Two died in twenty-six hours and the third on the sixth day after injection. The temperature of the first 2 rabbits gradually rose

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7. The animal was pronounced dead at the moment when respirations and all external muscular activity ceased.



4 or 5 degrees (F.) above normal in twelve to eighteen hours and then gradually receded without ever reaching the normal level. That of the third rabbit rose about 3 degrees (F.) in the first twenty-eight hours and then gradually declined, to reach its original level on the fourth day and 5 or 6 degrees (F.) below that at death.

The difference between the responses of the 2 rabbits which died in twenty-six hours and the 1 that died in six days was obvious. In the former an initial transient reduction in the heart rate was followed by a gradual rise to about 100 beats per minute above normal after several hours. The rate then dropped suddenly, and the electrocardiographic changes appeared. In 1 rabbit an elevated T wave appeared at twenty hours and was followed four hours later by an auriculoventric-

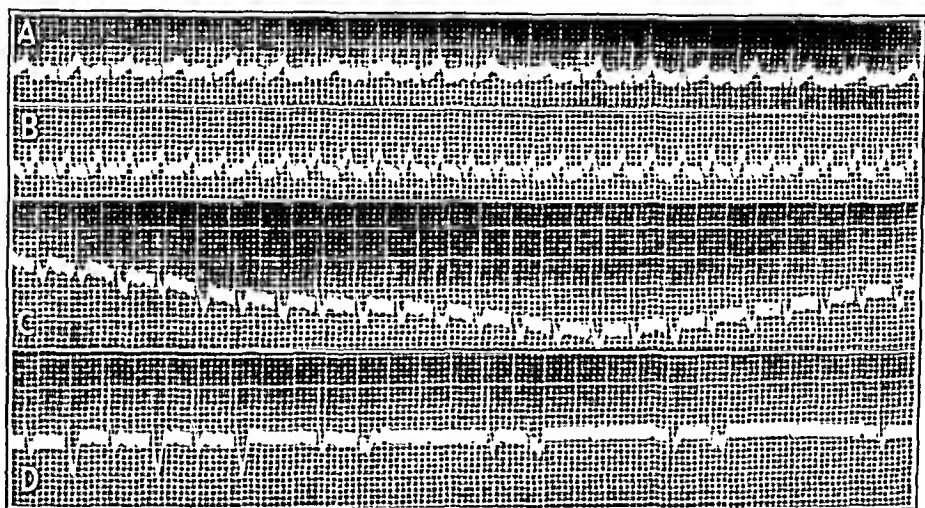


Fig. 1.—Electrocardiograms of rabbit 354, which was given an intravenous injection of staphylococcus exotoxin. The rabbit weighed 2,100 Gm. Respirations and muscular activity ceased eleven minutes after injection. *A*, before injection—rate, 186 per minute; *B*, five minutes after injection—rate, 310 per minute; *C*, nine and a half minutes after injection—rate, 242 per minute; *D*, ten minutes after injection.

ular block with numerous dropped beats which persisted until death. In the other rabbit a wandering pacemaker appeared at seventeen hours, and the T waves became markedly depressed about twenty minutes before death (fig. 2). The initial symptoms were lethargy and weakness, which progressed until the rabbit could no longer stand erect. Respirations became irregular and gasping. For a time before death typical running movements occurred and were followed by violent convulsions associated with opisthotonos and retraction of the neck.

The third rabbit had a gradual but moderate increase in the heart rate which reached its peak in twenty-four hours. This persisted until

the sixth day, when there was an antemortem slowing to almost the same level as before the injection. No significant electrocardiographic changes appeared. During the course of its illness the rabbit became increasingly weaker and ate little; on the sixth day it had a single mild uncharacteristic convulsive seizure and died. Postmortem examination revealed numerous abscesses in the heart, the lungs and the kidneys and a loss of weight of 530 Gm.

Immediately after receiving an intravenous injection of 2,500 units of staphylococcus antitoxin (Lederle Laboratories, Inc.), 1 rabbit received intravenously a lethal dose of washed toxigenic staphylococci. The administration of antitoxin was repeated at intervals until the animal had received 10,000 units in four days. During the first day the temperature rose to 106 F., where it remained for seven days, and then

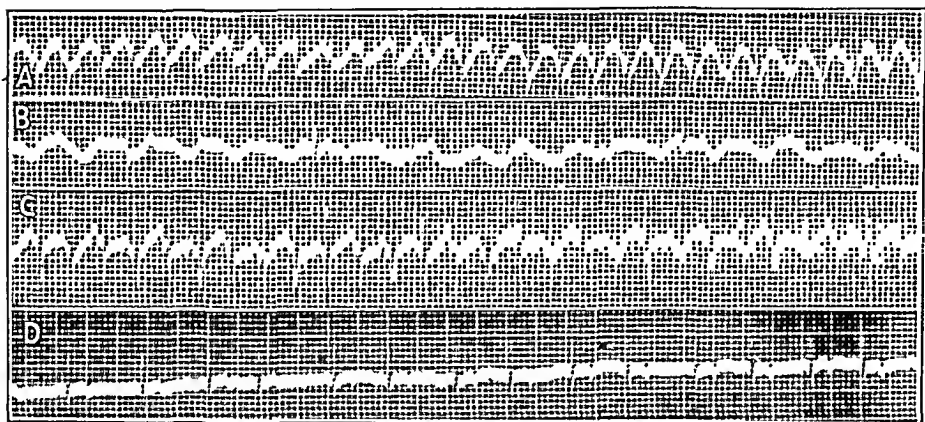


Fig. 2.—Electrocardiograms of 2 rabbits given intravenous injections of washed cultures of toxigenic staphylococci. In both animals respirations and muscular activity ceased twenty-six hours after injection. *A* (rabbit 342), ten and a half hours after injection—rate, 285 per minute (rate before injection, 236; weight, 2,300 Gm.); *B* (rabbit 342), twenty-three and a half hours after injection—rate, 111 per minute; *C* (rabbit 345), twenty-three hours after injection—rate, 288 per minute (rate before injection, 218; weight, 2,200 Gm.); *D* (rabbit 345) twenty-five and a half hours after injection—rate, 160 per minute.

receded toward normal. The heart rate rose little, and the rise was not maintained. There were no electrocardiographic changes. The rabbit appeared to be ill the first day after injection, and for the next twelve days it lost weight and became weaker. For the next three days the condition remained stationary. From then on it improved, and four months after injection the rabbit was well, having gained 400 Gm. over its original weight.

*Rabbits Receiving Washed Nontoxigenic Staphylococci.*—Six rabbits were given injections of washed cultures of the nontoxigenic staphylo-

coccus. Five died within fifteen to twenty hours and the other in fifty-eight hours and twenty-five minutes. The temperature was elevated 2 or 3 degrees (F.) above normal, and the heart rate increased 50 to 100 beats per minute. These changes followed no characteristic pattern. No significant electrocardiographic changes were observed. The rabbits became weak and lethargic in eleven to fourteen hours after injection. This condition increased until they could no longer stand erect. The respirations became more difficult and rapid. Death was gradual and quiet and was not associated with convulsions or any other characteristic muscular activity. During illness the rabbits lost from 170 to 260 Gm. in weight.

One cubic centimeter per kilogram of physiologic solution of sodium chloride was injected intravenously into 2 rabbits. No changes were observed in the temperature, the heart rate, the electrocardiograms or the general condition of the rabbits. Both were subsequently used in other experiments seven days later.

#### COMMENT

Nélis, Bouckaert and Picard<sup>1c</sup> demonstrated progressive drop in the blood pressure and slowing of the pulse rate followed shortly by ventricular fibrillation after the injection of staphylococcus exotoxin in the rabbit. This occurred before any respiratory changes and was the same in vagotonic as in normal rabbits. Dingle and co-workers<sup>4a</sup> demonstrated changes in the individual components of the electrocardiographic pattern which definitely indicated myocardial damage.

The electrocardiographic changes in the rabbits of our series which were given injections of exotoxin resembled those previously described sufficiently to require no further elaboration. Two of the 3 rabbits injected with toxin-free washed cultures of toxigenic staphylococci died within twenty-six hours, and their electrocardiograms showed changes similar to those of the rabbits receiving exotoxin, indicating the production of toxin in vivo. The other rabbit survived six days; during this time none of these changes appeared. It is significant also that there were no electrocardiographic changes either in the rabbit protected by antitoxin or in those given an injection of nontoxigenic staphylococci.

The characteristic chain of events which rapidly follows the intravenous injection of staphylococcus exotoxin<sup>3</sup> was seen in the 2 rabbits dying within twenty-six hours after the injection of washed toxigenic staphylococci, but it lasted over a longer period of time. The third rabbit died after six days of increasing debility and loss of weight, and at autopsy numerous abscesses were found. The rabbit given the injection of antitoxin became ill and debilitated but never showed any signs of

toxicity and finally recovered. Those rabbits dying of infection with washed nontoxigenic staphylococci died quietly and with none of the characteristics of toxicity.

Although no definite conclusions can be drawn from the changes in the pulse rate, the constancy of the pattern associated with exotoxin and the difference of the pattern when exotoxin is absent are worthy of further observation. The changes in temperature were insignificant.

These results confirmed the previous impression that the character of systemic disease due to staphylococci depends to a large degree in some instances on the reaction to exotoxin. In man the symptoms are so characteristic that the effect of the exotoxin can be readily recognized by the clinical picture of the patient.<sup>2d</sup>

#### SUMMARY

*Staphylococcus* exotoxin when injected intravenously into the rabbit rapidly produces a characteristic chain of clinical symptoms, with characteristic pulse and electrocardiogram.

These same changes are brought about over a longer period when washed cultures of toxigenic staphylococci are injected intravenously.

The intravenous injection of washed nontoxigenic staphylococci causes altogether different clinical symptoms and no changes in the electrocardiogram, although the rabbit may die within twenty-four hours after injection.

Drs. Harry Gold and Arthur M. Fishberg helped in interpreting the electrocardiograms.

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# PSEUDOHERMAPHRODITISM

## REPORT OF TWO CASES

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Of several classifications of patients with hermaphroditism that have been proposed to date, the most lucid and self-explanatory one is that of McCahey,<sup>1</sup> which is as follows: group 1, male pseudohermaphrodites without müllerian derivatives; group 2, female pseudohermaphrodites; group 3, true hermaphrodites; group 4, male pseudohermaphrodites with müllerian derivatives.

I wish to report on 1 patient representing group 2 and 1 representing group 4 and at the same time call attention to certain anatomic features characteristic of each of these four groups.

### MALE PSEUDOHERMAPHRODITES WITHOUT MÜLLERIAN DERIVATIVES

McCahey<sup>1</sup> gathered 12 reported cases of male pseudohermaphrodites without müllerian derivatives, and I have been able to add 7 more which have appeared in the literature subsequently.<sup>2</sup>

Patients in this group are unquestionably male; the identity of their sex is frequently confused by the presence of derivatives of the urogenital sinus rather than derivatives of the müllerian structures. The presence of a hypospadiac urethra, a vagina and labia-like structures is almost the rule. The testes are usually extraperitoneal although frequently atrophic. There is abundant clinical evidence of hypogonadism, such as atrophic prostate glands, beardlessness and a small penis. Mishell<sup>2a</sup> reported 3 cases in one family, in which the patients were 23, 32 and 35 years of age respectively and had lived together as sisters.

Inguinal hernias were associated with the condition in 6 of the 19 cases.

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From the Department of Surgery, St. Francis Hospital.

1. McCahey, J. F.: *Surg., Gynec. & Obst.* **67**:646, 1938.

2. (a) Mishell, D. R.: *Am. J. Obst. & Gynec.* **35**:960, 1938. (b) Carlisle, W. T., and Geiger, C. J.: *ibid.* **36**:1047, 1938. (c) Crossen, H. S.: *ibid.* **38**:123, 1939. (d) Rollins, P. R.: *Northwest Med.* **39**:181, 1940. (e) Palhares, C.: *Rev. de gynéc. et d'obst.* **2**:294, 1939.

## FEMALE PSEUDOHERMAPHRODITES

McCahey<sup>1</sup> reported 15 cases of patients in this group in 1938, and I have been able to accumulate 12 more case reports published since then.<sup>3</sup> To these I add a twenty-eighth case.

All of the patients in this group are genetically female; their chief disturbance is related to abnormal development of the urogenital sinus. The phallus is almost always large enough to be described as a penis and is the structure that usually attracts the attention of the parent or the physician, as it did in my case. The labia frequently have the appearance of a scrotum, and abnormalities of the vagina are frequent. In all cases the ovaries are located within the abdomen, and those examined histologically show normal ovarian tissue. Müllerian derivatives are usually present although frequently rudimentary. No derivatives of the wolffian body are seen. No instances of inguinal hernia are recorded. Stigmas of virilism, such as hirsutism, atrophic breasts, amenorrhea and masculine stature, are frequent.

## TRUE HERMAPHRODITES

McCahey described 17 cases of true hermaphrodites in November 1938.<sup>1</sup> However, Hugh Young in reporting his second case of a true hermaphrodite before the American Urological Society, on June 29, 1938,<sup>4</sup> considered 21 cases in the literature as confirmed and considered his second case as an acceptable twenty-second case. In May 1939, Smith and associates<sup>5</sup> reported what they considered to be the twenty-third and twenty-fourth proved cases, and I have obtained references to 7 more acceptable cases reported since that date.<sup>6</sup>

Patients in this group are supposedly bisexual persons with evidences of ovarian and testicular tissue, either as separate gonads or as an ovotestis with both kinds of germinal tissue in the same gonad. The

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3. Jones, H. O.: *Am. J. Obst. & Gynec.* **35**:701, 1938. Carlisle, W. T., and Geiger, C. J.: *ibid.* **36**:1047, 1938. Smith, C. K., and Stockwell, A. L.: *J. Urol.* **43**:234, 1940. Charvat, J.; Kodiceh, E., and Schubert, O.: *Endocrinology* **23**:91, 1938. Parhun, C. I.; Placinteanu, G., and Ornstein, I.: *Rev. franç. d'endocrinol.* **16**:344, 1938. Jasienski, G.: *J. d'urol.* **46**:562, 1938. Miller, I. D., and Kenny, P. J.: *Brit. J. Surg.* **27**:728, 1940. Garcia, A. L.: *Semana méd.* **1**:1457, 1938. da Rocha, J. M.: *Hospital, Rio de Janeiro* **15**:313, 1939. Pereira, A.: *Rev. urol. de São Paulo* **4**:169, 1937.

4. Young, H. H.: *Operative Treatment of True Hermaphroditism: New Technic for Curing Hypospadias*, *Arch. Surg.* **41**:557 (Aug.) 1940.

5. Smith, P. G.; Mack, J. R., and Murray, M.: *J. Urol.* **41**:780, 1939.

6. Kell, R. C.; Matthews, R. A., and Bockman, A. A.: *Am. J. M. Sc.* **197**:825, 1939. Reinberger, J. R., and Simkins, C. S.: *Am. J. Obst. & Gynec.* **36**:275, 1938. Seligman, B.; Kraushar, S., and Byron, C. S.: *J. Clin. Endocrinol.* **1**:429, 1941. Doss, A. K., and Priestley, J. T.: *Am. J. Obst. & Gynec.* **43**:859, 1940. Jasienski, G.: *J. d'urol.* **46**:456, 1938. Malgras and Gricouroff: *Mém. Acad. de chir.* **65**:272, 1939.

müllerian derivatives are usually well differentiated although frequently underdeveloped; at the same time, wolffian derivatives in an abortive state of development are encountered just as frequently. The urogenital sinus usually shows the same type of disturbed development as it does in a female pseudohermaphrodite, namely, the frequent development of a penile phallus, a scrotum and a communication of the vagina with the posterior urethra.

The presence of 13 inguinal hernias in the collected group of 31 true hermaphrodites requires additional comment in view of the fact that the hernial sac frequently contains the gonad, either ovarian or testicular in nature or both. McCahey suggested that the migratory tendency of testicular tissue might be the explanation for the high incidence of inguinal hernias in this group.

#### MALE PSEUDOHERMAPHRODITES WITH MÜLLERIAN DERIVATIVES

McCahey contributed 23 cases of male pseudohermaphrodites with müllerian derivatives in 1938,<sup>1</sup> and I have collected references to 8 more reported since that date.<sup>7</sup> To these I wish to add a case of my own, making a total of 32 cases.

Patients in this group are generally considered genetically male; in them all gonadal tissue is testicular. Development of the müllerian duct system is rather extensive, and the presence of a complete internal female reproductive tract including everything but the ovary is not unusual. Wolffian derivatives develop alongside those of the müllerian system. The abnormal development of the urogenital sinus is usually limited to a rudimentary vagina which communicates with the posterior urethra or ends blindly within the perineum. The testicle frequently occupies the position of an ovary as far as its relation to the uterus and the surrounding structures is concerned.

Inguinal hernias were present in 10 of the 32 cases, and the hernial sac frequently contained a descended testicle. The secondary sexual characteristics were more frequently male than female.

The case to be presented here was that of a male pseudohermaphrodite with müllerian derivatives. To my knowledge this is the thirty-second confirmed case of its kind to appear in the literature.

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7. Pratt, J. P.: *Am. J. Obst. & Gynec.* **40**:780, 1940. Weisman, A. L., and Schwarz, A.: *Intersexuality Proved by Operation and Microscopic Examination*, *J. A. M. A.* **117**:2248 (Dec. 27) 1941. Nilson, O.: *Acta chir. Scandinav.* **83**:231, 1939. Greenhill, J. P., and Schmitz, H. E.: *West. J. Surg.* **48**:36, 1940. Barbers, J. C.: *Bol. Soc. de cir. de Rosario* **5**:125, 1938. Geissler, J.: *Beitr. z. path. Anat. u. z. allg. Path.* **99**:305, 1937.

## REPORT OF CASES

The patient was 18 years old, white and male. He entered the hospital and the service of Dr. E. C. McGill for the repair of an indirect inguinal hernia on the left side. He was first made aware of the presence of this a week before, when he noted sharp pain and swelling in his left groin on lifting a heavy weight at the steel mill where he was employed as a buffer. The swelling was about the size of a plum, and it together with the pain disappeared when the patient lay down. In the course of the following week on coughing or straining, he had recurrences of the pain and the swelling in the left groin.

The inventory by systems revealed that he had always enjoyed fine health and was regarded by his family and friends as a well developed muscular youth. He had become a manual laborer on graduating from high school. He had no further pertinent complaints relative to his illness on admission. Later, on direct questioning, it was learned that he had never shaved, although his face was covered with a fine growth of hair, which he did not think required shaving. His stature and chest development were masculine; in fact, he had been complimented on his excellent masculine physique. He had a male escutcheon and a well developed penis. He described having erections of the penis and nocturnal pollutions but was noncommittal as to having had intercourse. He did have many female friends, who were seen to visit him during his subsequent convalescence. He was aware of an undescended right testicle for which he never sought medical advice and was under the impression that his left testicle was normal and had always been in the scrotum.

His past medical history was noncontributory except that he had had measles as a child but did not remember having mumps. The familial history was normal; apparently there were no other hermaphrodites in the family.

Physical examination revealed a well developed, well nourished, muscular white youth in good health. The temperature on admission was 98 F.; the pulse rate was 76, and the respiration rate was 20. Examination of the head and the neck revealed nothing significant. His haircut was that of a man, and the bearded zone of his face was covered with a fine growth of hair which was slightly coarser over the upper lip. The chest revealed normal male breasts with well developed pectoralis muscles and good chest expansion. The heart and the lungs were normal on examination. The blood pressure was 130 systolic and 80 diastolic (expressed in millimeters of mercury), and the pulse was regular and of normal quality. The abdomen was scaphoid with well developed musculature, a narrow waistline and a distribution of hair over the pubis extending up to the navel corresponding to the usual male pattern. The abdomen was nontender, and no viscera could be palpated. On standing and coughing a mass about 4 cm. in diameter entered the left inguinal canal at the internal inguinal ring and protruded just outside the external inguinal ring. An impulse was transmitted on coughing, and the external ring was about 2 cm. in diameter. The hernial sac was thought to contain omentum, which might have produced the slight tenderness experienced on palpation over the unreduced sac. The penis was somewhat larger than the average male adult penis, and the right testicle was not present in the scrotum and could not be palpated within the right canal. The left testicle appeared considerably enlarged (twice the average size) and was in the scrotum. The scrotum showed no abnormalities. The urethra appeared normal, and the right external inguinal ring did not permit introduction of the examining finger. On rectal examination a smooth, small, trilobed prostate gland was palpated and was thought to be normal; no rectal or pelvic masses could be palpated, and the seminal vesicles felt normal to palpation.



The blood count revealed 4,790,000 erythrocytes, 5,350 leukocytes and 89 per cent hemoglobin. A differential leukocyte count showed 60 per cent polymorphonuclear leukocytes, 31 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The urine had a specific gravity of 1.025 and gave negative reactions for albumin, sugar and acetone; the centrifuged specimen revealed nothing significant. The patient was prepared for left herniorrhaphy with the preoperative diagnosis of a left indirect inguinal hernia (reduceable) and a right undescended testicle. There was no clinical suggestion of hermaphroditic pathologic change.

With the patient under anesthesia induced with ether and ethylene, a classical left Bassini incision was made. The aponeurosis of the external oblique abdominal muscle was divided down to the external inguinal ring, the spermatic cord and the hernial sac were identified, and the dissection of the sac was accomplished in the usual manner. As the internal inguinal ring was approached, it was observed that traction on the spermatic cord consistently drew a large firm tumor mass through the internal ring into the hernial sac; relaxation of the cord permitted the tumor mass to return to its position within the peritoneum. The sac was then opened, and the vas deferens and an additional cordlike structure were seen just beneath the peritoneum of the sac. By traction on these structures the specimen shown in figure 1A was brought into view, being delivered through the internal ring. It was at once apparent that an internal female reproductive tract was being dealt with. To investigate the possibility of a communication between the lowermost portion of the uterus (or possibly of a vagina) with the bladder or the posterior part of the urethra, the uterus was opened and a probe passed down through its lumen; it was found to end blindly in the vesicorectal perineum. Another catheter passed through the urethra into the bladder demonstrated the independence of these two structures. The left testicle was then delivered from its scrotal position and on inspection was found to be at least twice the average size of normal testes and obviously hypertrophic. The missing right gonad was attached to a broad ligamentous structure much in the relation of an ovary to its surrounding structures.

The problem then arose as to what the fate of these müllerian derivatives with the attached gonad should be. If the gonad were an ovary, then in view of the patient's preponderant male secondary sexual characteristics, it should be resected. If it were an atrophic testicle, which was more likely because of the right-sided cryptorchidism and the smooth dense tunica, it would also be best if it were removed. First of all, it was apparently functionless as a testicle, and second, in its intra-abdominal position it was predisposed to neoplastic change. Furthermore, no connecting epididymis or vas deferens for this gonad could be demonstrated at the time of operation. On the other hand, a well outlined vas deferens and epididymis were identified for the left testicle, running up the spermatic cord, adherent to the left side of the uterine fundus and then continuing down toward the neck of the bladder. It was therefore decided to remove the uterus and its appendages and the right gonad after dissecting the left vas deferens free of the uterus. The point in the perineum where the blind uterine cervix was dissected away was peritonealized with the posterior reflection of the bladder peritoneum. The hernia was then repaired in the usual manner with the transplantation of the spermatic cord above the aponeurosis of the external oblique muscle.

The patient made an uneventful postoperative convalescence. Although further history and examination were obtained, neither he nor his family was made aware of his pseudohermaphroditic state. I was able to procure as much information as

necessary on the basis of his cryptorchidism. Furthermore, inasmuch as it was intended for him to remain male, all therapy having been directed toward that end, I had no desire to create doubt in a mind that probably could not fathom such developments.

*Gross Pathologic Examination* (Drs. O. T. Schultz, pathologist, and A. Lapi, resident pathologist).—The gross appearance of the specimen suggested an internal female reproductive tract with an amputated left cornu (fig. 1A). The uterus measured 5.5 by 7 by 2 cm. The perimetrium was smooth and glistening. The

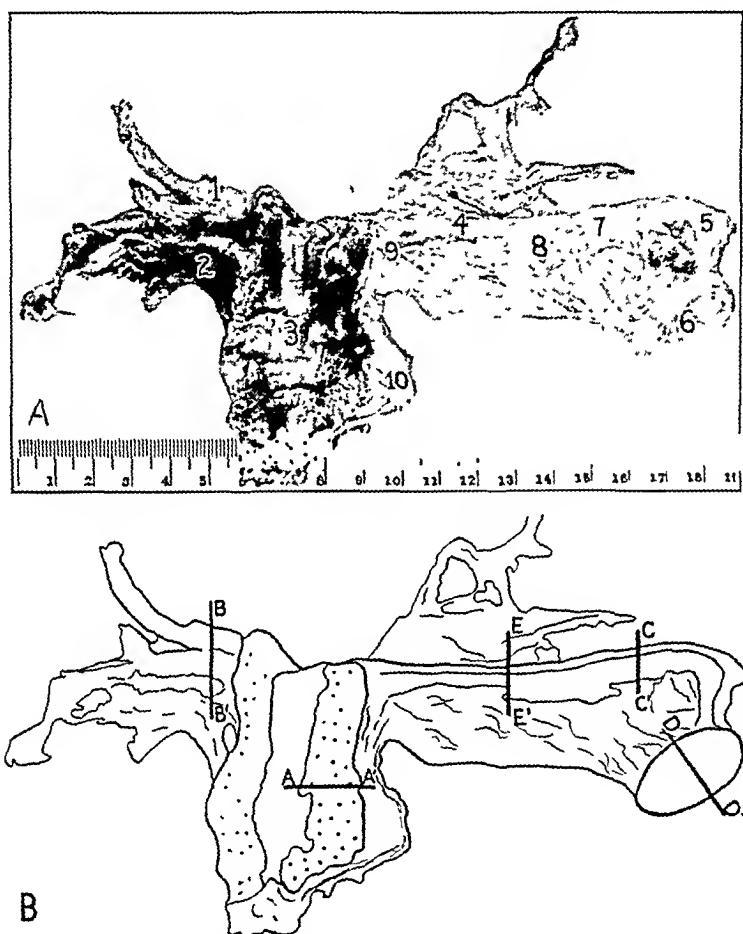


Fig. 1.—A, photograph of the operative specimen removed from the male pseudohermaphrodite after fixation in solution of formaldehyde. It has the appearance of an internal female reproductive tract with an amputated left cornu. The uterine fundus has been opened. The arabic numerals identify the following structures: 1, the left fallopian tube; 2, the groove in which the left vas deferens was adherent; 3, the uterine fundus; 4, the isthmus of the right fallopian tube; 5, the ampulla of the right fallopian tube; 6, the right cryptorchid gonad which proved to be a testis; 7, the head of the epididymis; 8, the body and the tail of the epididymis; 9, the ductus epididymidis; 10, the right vas deferens. B, drawing of the specimen shown in A indicating areas shown in the photomicrographs: A—A', figure 2; B—B', figure 3; C—C', figures 4 and 6; D—D', figures 5; E—E', figure 7.

wall of the fundus uteri averaged 1 cm. in thickness and thinned out to 2 or 3 mm. near the lower uterine segment. No structure anatomically resembling the cervix could be demonstrated, the uterine fundus apparently having ended blindly. There was no evidence of a vagina. The uterine cavity was lined by a smooth pale tan mucous membrane averaging 1 mm. in thickness. No communication existed between the lumen of the uterine fundus and the lumens of what were thought to be fallopian tubes. Along the left side of the fundus was a grooved channel which represented the former position of the left vas deferens. Occupying a similar position beneath the serosal surface of the right side of the uterus was another tortuous tubular structure which histologically proved to be the right vas deferens.

At the left cornu of the uterus several amputated cordlike structures were found. The uppermost one was 3 mm. in diameter and had a slitlike lumen. This later proved to be the isthmus and the intramural portions of the left fallopian tube (fig. 3). The remainder of the cornu was made up of bands of fibrous tissue and smooth muscle in which a rich plexus of blood vessels was located.

A relatively thick broad ligament extended to the right of the uterus for a distance of 10 cm. It was 3.5 to 4 cm. in width and up to 8 mm. in thickness in some areas. Between its two peritoneal surfaces lay several tubular structures and blood vessels. The tubular structure coursing along the top border of this broad ligament appeared to be the right fallopian tube (fig. 4). It had a lumen in the center which expanded toward the peripheral end. The ostium of the tube pointed toward the gonad but was embedded in membranes continuous with the broad ligament. The caliber of the entire tube was much less than normal. Beneath and below the right fallopian tube and following the latter along its distal two thirds a structure resembling a mesonephric body was dissected out between the layers of the broad ligament. It measured 5 cm. in length and averaged 6 mm. in width and 3 mm. in thickness. It consisted of narrow tortuous tubules which on histologic examination proved to be the head of the epididymis (fig. 6).

At a point midway in the broad ligament a well outlined tortuous tubular structure was exposed which appeared to be continuous with the tubular mass already mentioned and appeared to be the body and the tail of the epididymis. Leading away from this was a still larger tube which gradually appeared to uncoil itself, so that by the time it reached the right side of the uterus it had all the gross appearances of the right vas deferens. This structure averaged 2 mm. in diameter and histologically resembled the vas deferens.

The gonad was firmly attached to the broad ligament along one of its longitudinal surfaces for a distance of 3 cm. by a short suspensory ligament which fused with the capsule of the testis. The gonad measured 3 by 2 by 2 cm. and was covered by a smooth thickened tunica albuginea. On section it had the yellow-tan granular appearance of testicular tissue. The gonad presented a small corpus highmorianum which subsequently proved to contain rete testis. On gross inspection no tissue representing the head of the epididymis could be demonstrated in contact with the posterior pole of the testis. Within the layers of the suspensory ligament attaching this pole of the testis to the broad ligament, tubules, which on histologic examination suggested remnants of mesonephric tubules, were found, but nothing was observed suggesting either an epididymis or a ductus deferens.

*Microscopic Pathologic Examination.*—Sections taken through the uterine fundus at various levels revealed a thin atrophic endometrium, a thick myometrium and a normal perimetrium (fig. 2). The surface of the endometrium was everywhere denuded of its epithelium. It consisted of a compact stroma in which a small

number of simple tubular glands were seen intermingled with a larger number of engorged capillaries and larger blood vessels. In some areas there was a localized extravasation of red blood cells. The glands were lined by tall columnar epithelium. The nuclei were elongated and rested against the basement membrane so that the cells presented a distal free border. An occasional gland branched at its blind end, and still less frequently an acinus was found near the myometrium. The myometrium consisted of interlacing bundles of smooth muscle and fibrous connective tissue interspersed with occasional large blood vessels. Sections through the lower uterine segment of this organ failed to reveal anything that suggested an anatomic dif-



Fig. 2. (*A—A'* in fig. 1 *B*).—Photomicrograph of a section through the uterine fundus (iron-hematoxylin stain;  $\times 60$ ). Note the endometrial surface denuded of epithelium, the engorged blood vessels, the simple tubular glands, the area of extravasated erythrocytes and the myometrium.

ferentiation into a cervix. All the sections indicated a quiescent endometrium in a hypoplastic uterus.

Sections through the left cornu of the uterus revealed the intramural portion of the left fallopian tube (fig. 3), below which was found a broad layer of tissue consisting of smooth muscle, fibrous tissue and numerous blood vessels. The smooth muscle represented an extension of the musculature of the fundus. Frequent sub-serosal extravasations of erythrocytes were seen. Sections through the fallopian tube (fig. 3 *A* and *B*) showed a tubular structure with flattened epithelial folds and a slitlike lumen. The epithelium was pseudostratified. All nuclei were of a

similar vesicular appearance with their longest axis lying in the vertical diameter of the cell. The musculature surrounding the epithelium consisted of two thick layers of smooth muscle because of its proximity to the fundus.

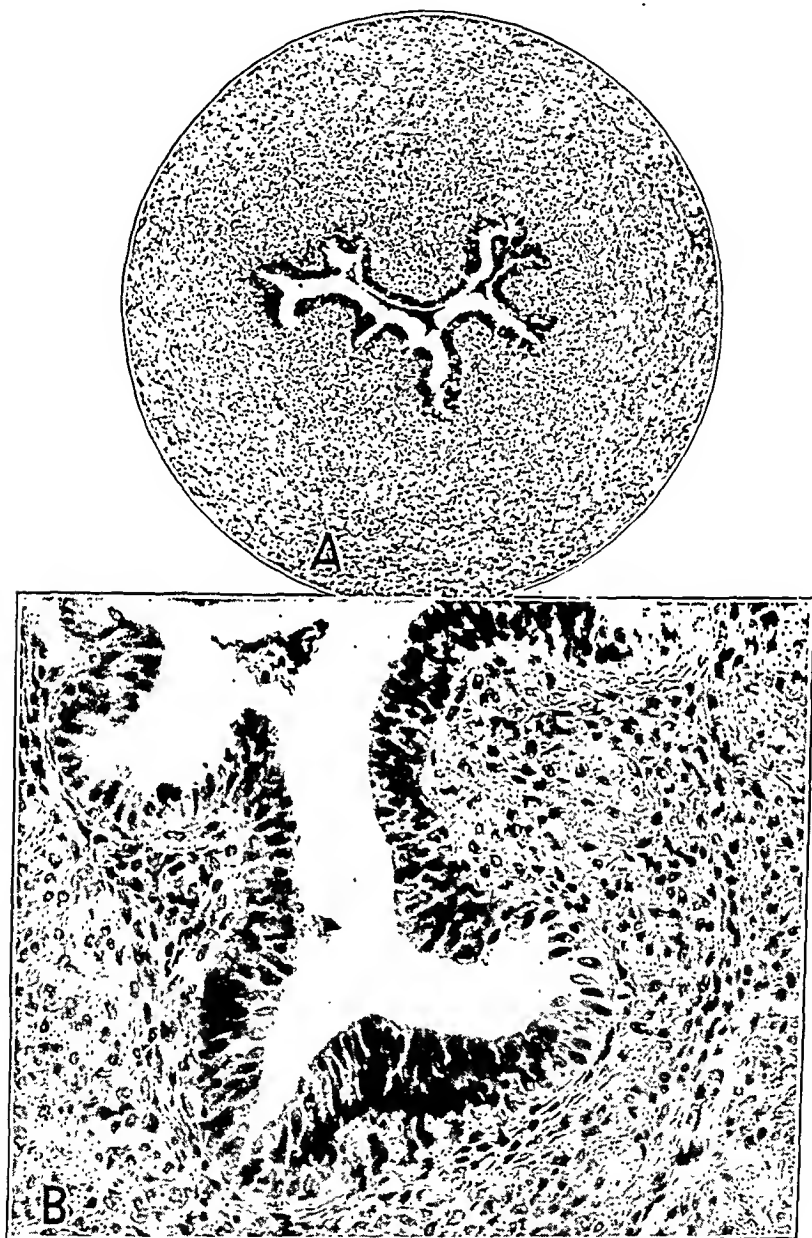


Fig. 3 (*B—B'* in fig. 1 *B*).—*A*, photomicrograph of a section through the intramural portion of the left fallopian tube (iron-hematoxylin stain;  $\times 40$ ). Folds of mucous membrane are flattened, and the lumen is slitlike. Note the inner layer of circular muscle and the outer layer of the longitudinal muscle. *B*, higher magnification of glandular epithelium shown in *A* (iron-hematoxylin stain;  $\times 200$ ).

Sections through the ampullary portion of the right fallopian tube (fig. 4) revealed a lumen which was partitioned off by numerous wide and narrow epithelial folds. The epithelium consisted of a single layer of tall columnar cells with large cylindric nuclei which filled most of the cytoplasm. Two layers of smooth muscle immediately surrounded the epithelium except in the areas of broad epithelial folds. In the latter a dense layer of fibrous tissue intervened and made up the interior of the fold. Sections through the isthmus of the right fallopian tube had appeared similar to the intramural portion of the left fallopian tube. Here the epithelial folds were flatter, the epithelium was more apt to be pseudostratified; the lumen, slitlike, and the muscle coat, thicker.

Sections through the right gonad (fig. 5 *A* and *B*) revealed shrunken seminiferous tubules lined by one or more layers of epithelial cells resting against a



Fig. 4 (*C—C'* in fig. 1 *B*).—Photomicrograph of a section through the ampulla of the right fallopian tube (hematoxylin-eosin stain;  $\times 52$ ). Note the numerous epithelial folds and the thin muscular coat.

thickened basement membrane. Cytologic examination of these cells indicated that they almost all possessed similar vesicular ovoid nuclei the chromatin content of which was usually aggregated in one centrally placed nucleolus. The cell outline was frequently rectangular and made up of a finely reticulated cytoplasm. The lumens of many tubules were filled with a similar type of material. No mitoses were seen. Practically all of these cells were of this type and appeared to be Sertoli cells. No cells of the spermatogenic series were seen. The interstitial tissue between seminiferous tubules was made up of loose connective tissue which in many areas was homogeneous and pink staining, and in others, vacuolated. Aggregates of large polyhedral cells arranged in epithelioid groups were prominent. These cells contained spherical nuclei with eccentrically placed nucleoli; the center of the nucleus

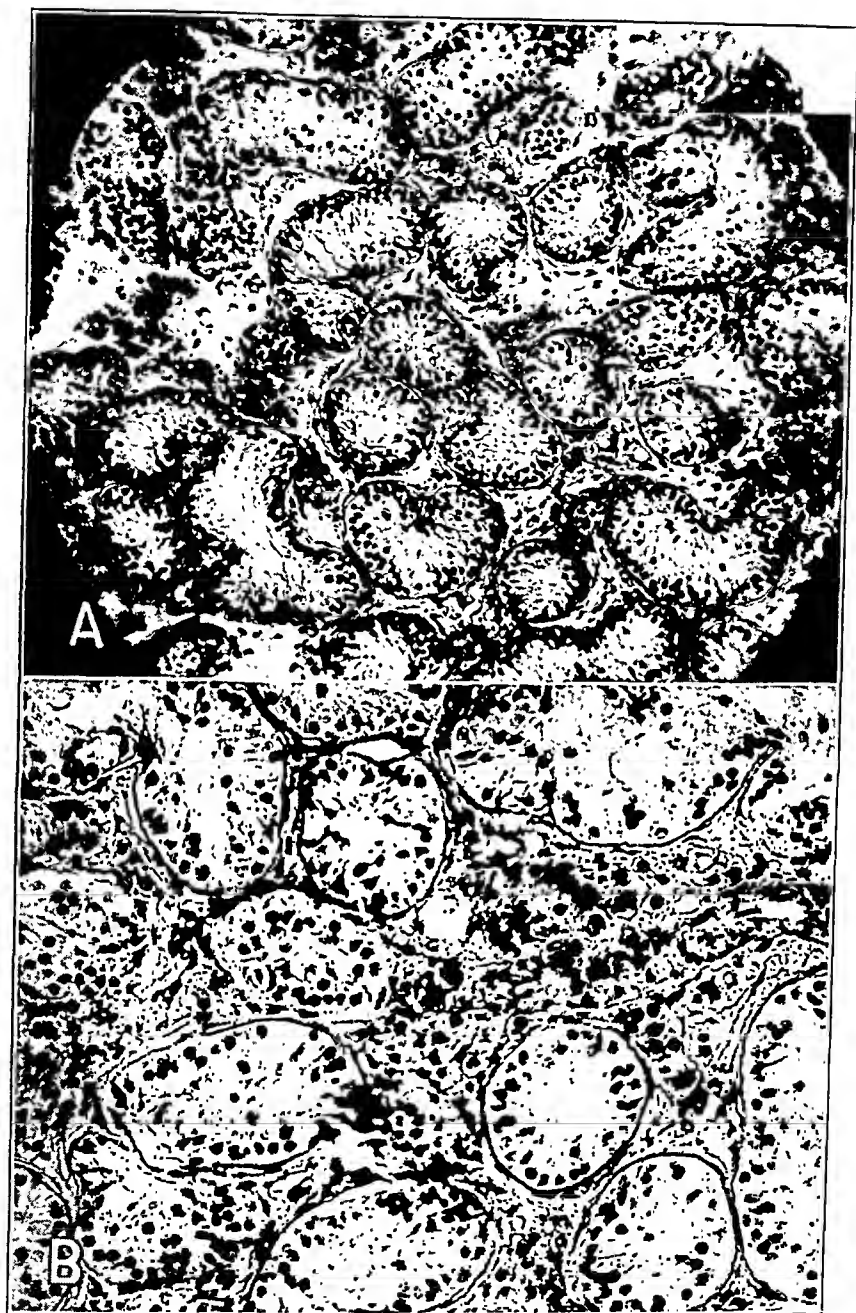


Fig. 5 (*D—D'* in fig. 1 *B*).—*A*, photomicrograph of a section through the right cryptorchid gonad showing atrophic seminiferous tubules (iron-hematoxylin stain;  $\times 110$ ). Note that the epithelial cells are frequently only one row in depth and that all of these cells appear to be of the same type (Sertoli cells). Albuminous material fills the lumen of many tubules. Interstitial areas show frequent areas of hyaline and vacuolar degeneration. *B*, higher magnification of a field adjoining that shown in *A* (iron-hematoxylin stain;  $\times 170$ ). Note the uniformity in the type of epithelial cell (Sertoli cells) and the prominence of the interstitial cells of Leydig. Note the absence of all forms of spermatogenic cells.

was frequently clear with its chromatin granules scattered in the periphery and one or two nucleoli adjoining the clear zone in the center. The cytoplasm of these cells was abundant and granular and contained inclusion bodies. They were undoubtedly

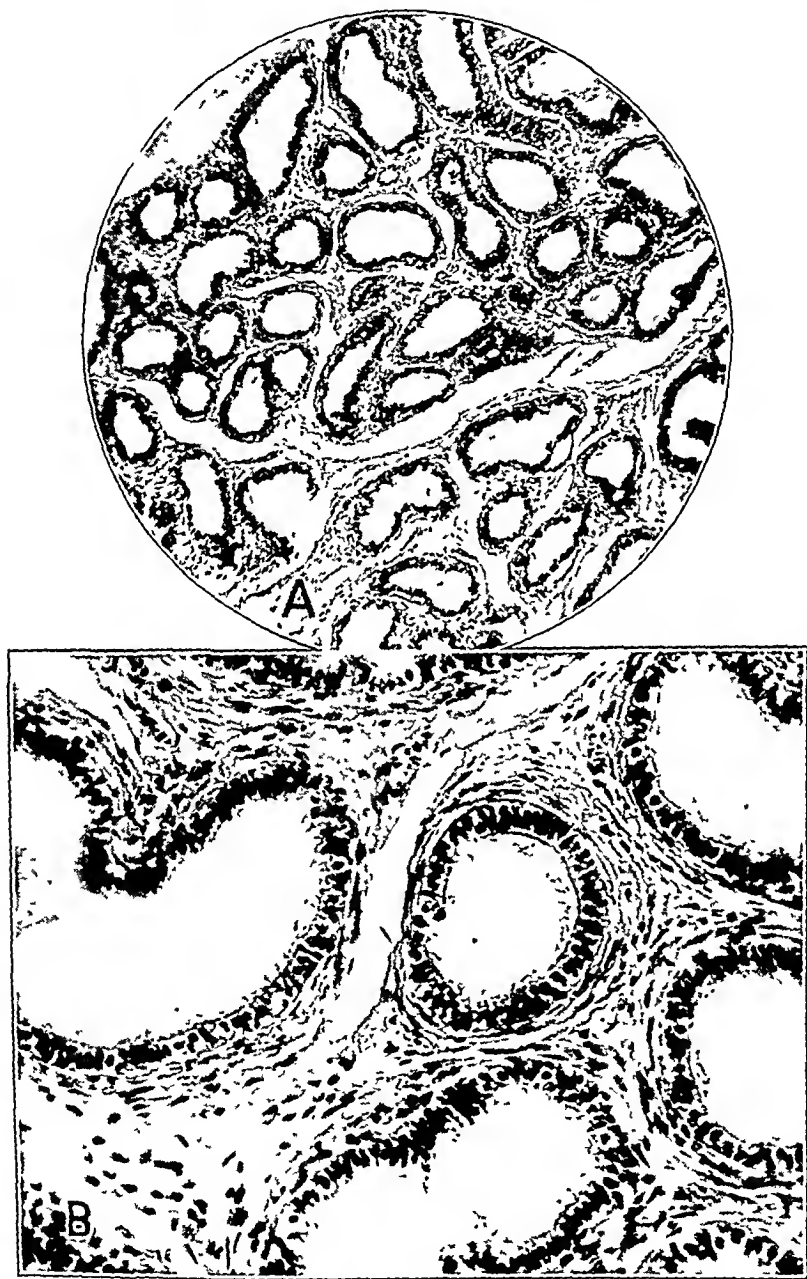


Fig. 6 (*C—C'* in fig. 1*B*).—*A*, photomicrograph of a section through the head of the right epididymis showing lobules of acini separated by septums of smooth muscle and connective tissue (hematoxylin-eosin stain;  $\times 44$ ). *B*, higher magnification of *A* showing columnar epithelium, brushlike borders on the distal free margins of the epithelial cells and the interacinar structure (hematoxylin-eosin stain;  $\times 170$ ).



interstitial cells of Leydig. Their prominence here was considered a relative hyperplasia due to the comparative atrophy of the seminiferous tubules.<sup>8</sup>

At the hilus of the testicle and lying within the tunica albuginea were large dilated tubules which formed irregular anastomosing channels which were lined by a single layer of cuboid cells. These were the rete testis.

Within the suspensory ligament of this gonad several epithelial-lined tubules without lumens were observed which may have been remnants of mesonephric tubules, for they did not resemble histologically the efferent ductules of the head of the epididymis. The tunica albuginea was a thick dense layer of fibrous connective tissue.

Sections taken through the head of the epididymis (fig. 6 *A* and *B*) revealed a lobulated structure made up of large acini lined by tall columnar or pseudocolumnar epithelium. The nuclei filled most of the cell and the distal margins of the cell had a brushlike border. The lumens of the acini were empty. The individual acini were separated by thin layers of smooth muscle and connective tissue.

Sections through the body of the epididymis (fig. 7 *A* and *B*) showed many tortuous branches of the coiled ductus epididymis. The duct was lined by pseudostratified columnar epithelium made up of two distinctly different types of cells. Along the basement membrane a discontinuous row of cuboid cells filled by small round densely staining nuclei were seen. Above this the cells were tall columnar in type with large ellipsoid vesicular nuclei. Brushlike borders were present along the free distal margin. The duct was surrounded by a dense circular and longitudinal layer of smooth muscle. Sections through the tail of the epididymis revealed the same histologic appearance. Sections through the vas deferens were the same except that the epithelium was lower, the folds were flatter, no brushlike borders were seen on the free surfaces of the epithelial cells, and the muscle wall was much thicker.

The patient whose case I have just presented was typical of the group McCahey described as male pseudohermaphrodites with müllerian derivatives, although there were no female remnants of a urogenital sinus. The fact that in about one third of all cases of hermaphroditism, with the exception of those of female pseudohermaphroditism, there is an associated inguinal hernia is a fact not to be dismissed too lightly. It might warrant more frequent intra-abdominal exploration of the hernial sac in clinical cases of associated cryptorchidism and hypogonadism as well as in the cases of the more obvious hermaphroditism. The frequent occurrence of inguinal hernia in these cases is attributed to the inherent tendency of testicular tissue to leave the peritoneum.

The specimen showed a rather extensive development of the müllerian duct system; it further demonstrated in a rather convincing manner the embryonic development of the müllerian and wolffian duct systems alongside of each other. In normal development one of these two duct systems should have atrophied, depending on the sex of the germinal tissue. The explanation that is most frequently offered for the persistence of the

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8. Maximow, A. A., and Bloom, W.: Textbook of Histology, Philadelphia, W. B. Saunders Company, 1940.

müllerian duct derivatives in a case such as this is that there was inadequate testicular development. Adequate testicular tissue is supposed to cause atrophy of the müllerian ducts. This is unlikely because testicular

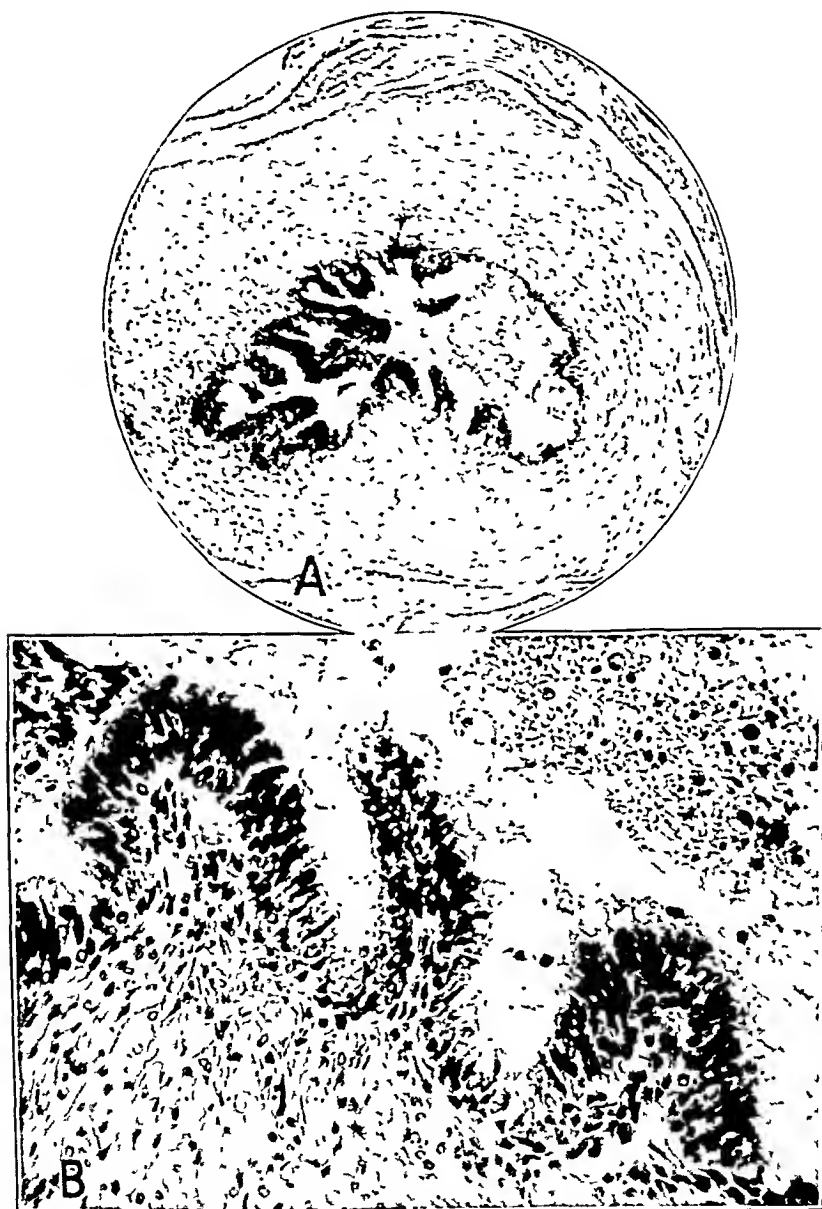


Fig. 7 (*E—E'* in fig. 1 *B*).—*A*, photomicrograph of a section through the body of the right epididymis showing a tortuous ductus epididymitis and its thick smooth muscle wall (iron-hematoxylin stain;  $\times 22$ ). Note that the lumen of the duct is filled with secretion material. *B*, higher magnification of *A* (iron-hematoxylin stain;  $\times 200$ ). Note the epithelial cells with small densely staining round nuclei nearest the basement membrane and the tall columnar cells with ellipsoid vesicular nuclei and brushlike distal margins superficial to the basement membrane. The lumen of the duct contains cast-off epithelial cells and secretion droplets.

function was sufficient in this instance to have developed a normal penis, a male scrotum, a normal left testicle, a normal prostate and normal male secondary sexual characteristics. Furthermore, if there was testicular insufficiency present here one might reasonably anticipate the presence of some female remnants of the urogenital sinus, such as a bifid scrotum, rudimentary vagina or hypospadiac urethra. McCahey<sup>1</sup> expressed the opinion that the development of the urogenital sinus is definitely under the control of the gonads.

A more tenable explanation than inadequate testicular development was offered by McCahey and is in keeping with what is known about the embryonic development of the gonad. The primordial gonad tissue is a testicle, and if ovary is to develop, it does so as a layer of cortical tissue which surrounds the original testicle and eventually replaces it. In a case such as the one just reported it is proposed that ovarian tissue was present at some time but was later replaced by testicular tissue expanding into the periphery.

The solution to the problem in this case was fortunately a simple one, for there was little reason to consider the patient, from a clinical point of view, as anything but male. It might be argued that the derivatives of the müllerian duct in no way interfered with his function as a male; this would be true were it not for the concern now taken toward the fate of testicular tissue within the abdomen. Certainly the intra-abdominal testis could serve no useful function, and the patient was not dependent on it for his source of androgenic hormone.

Since preparing the foregoing report, another case of a female pseudo-hermaphrodite has been brought to my attention through the courtesy of Dr. Dwight F. Clark, of Evanston, Ill. This is the twenty-eighth case of its kind in the literature.

The patient was a 23 year old white woman, who was aware of having a penis since childhood. Her parents had been told she would "bleed to death" if surgical amputation were attempted. The child reconciled herself to her fate by shunning the company of other children, thinking she was "different" from other girls. She even went to the point of developing physical aptitude so that she could assist her father with the manual labor on the farm. When she became 14 years of age and had not commenced to menstruate, she became all the more convinced that she was "different" and denied herself ordinary social contacts. She graduated from high school with excellent grades and was treated by her classmates as a thoroughly feminine personality.

When the patient was first brought to her physician, she was sullen and antagonistic, as though she were trapped and discovered against her will. After reassurance that she could be helped, she became more cooperative. The majority of her secondary sexual characteristics were feminine; however, she did have masculine breasts and a moderate increase of pubic hair over the abdomen. She had a feminine alto voice. Routine taking of the history and physical examination added nothing more, and detailed pelvic examination was done with the patient under anesthesia.

A fully developed penile structure  $3\frac{1}{2}$  inches (8.9 cm.) in length was present, with a glans penis and a prepuce (fig. 8). A dimple was present at the tip of the glans, but there was no external urinary meatus. A hypospadiac external urethral meatus was present in the midline between the frenulum of the glans and the anterior fourchet of a small vaginal introitus. Scrotal-like labial folds were present

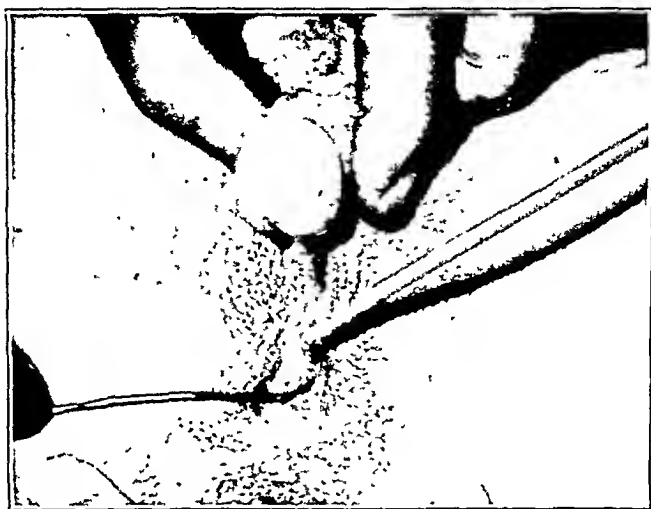


Fig. 8.—Photograph of the external genitalia of the 23 year old female pseudohermaphrodite. The  $3\frac{1}{2}$  inch (8.9 cm.) penile structure does not contain a corpus cavernosum urethrae or a urethra. A rubber catheter has been inserted into the hypospadiac external urinary meatus. A metal probe has been inserted into the vaginal introitus.

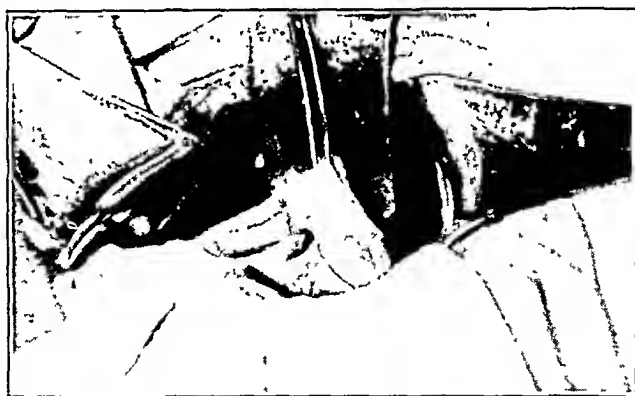


Fig. 9.—Photograph taken at the time of exploratory laparotomy. This revealed a rudimentary uterus 2 inches (5 cm.) long with a rudimentary right fallopian tube and a round ligament. No derivatives of the müllerian duct were present on the left side. No ovarian or testicular tissue could be demonstrated.

on each side of the penis and became confluent at the level of the urinary meatus. The vagina was a tubular organ which accommodated the index finger for its full length and width.

Exploratory laparotomy was then carried out, and in the right adnexa a rudimentary right half of the uterus about 2 inches (5 cm.) in length was identified (fig. 9). Extending to the right of it was a hypoplastic right fallopian tube about 3 inches (7.6 cm.) in length and attached to a broad ligament. The right round ligament became confluent with the intramural portion of the fallopian tube. No similar müllerian derivatives could be found for the left adnexa. Moreover, no evidence of either ovarian or testicular tissue could be demonstrated in the explored portions of the pelvis and the abdomen.

For cosmetic reasons the penile structure was resected flush with the perineum, and the scrotal folds were removed (fig. 10). Histologic sections of the body of the penis revealed a corpus cavernosum penis but no corpus cavernosum urethrae or urethra. This implies that the amputated structure was really a hypertrophied clitoris rather than a true penis.

The patient had an uneventful convalescence and on leaving the hospital was encouraged, happy and grateful.



Fig. 10.—Photograph taken after amputation of the penile structure. Black silk drains emerge from either angle of incision.

#### SUMMARY

The thirty-second case of a male pseudohermaphrodite with müllerian derivatives is reported. The genital tract of this 18 year old male patient consisted of a normal penis, a prostate, a seminal vesicle, a scrotum, and a left testicle with its epididymis and a vas deferens. A well developed uterus with bilateral normal fallopian tubes and one broad ligament was present. Attached to the broad ligament was an intra-abdominal right testis and a right vas deferens and epididymis which did not communicate with the right testis.

The twenty-eighth case of a female pseudohermaphrodite is reported. The external genitalia of this 23 year old female patient consisted of a penis with a glans and a prepuce, scrotal-like labial folds, a hypospadiac

external urethral meatus and a rudimentary vagina. The internal genitalia consisted solely of a rudimentary right half of the uterus, a right fallopian tube and a broad and a round ligament. Nothing was present in the left adnexa, and no gonadal tissue could be found on exploration.

The numbers of reported cases of each of four types of hermaphrodites are brought up to date.

The advisability of intra-abdominal exploration of the hernial sac in cases of hernia associated with hermaphroditism, hypogonadism or cryptorchidism is emphasized because of the high incidence of inguinal hernias associated with such deformities.

St. Francis Hospital.

# BLOOD PRESSURE CHANGES DURING SPINAL ANESTHESIA IN NONOPERATIVE CASES

HARRY KOSTER, M.D.

BROOKLYN

The fall in blood pressure which all observers agree is commonly found accompanying spinal anesthesia has been ascribed in the main to two causes: (1) dilatation of the arterioles in the anesthetized area due to a block of vasoconstrictor fibers in the anesthetized roots<sup>1</sup>; (2) decreased cardiac output.<sup>2</sup>

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From the Crown Heights Hospital.

1. (a) Bradshaw, H. H.: The Fall in Blood Pressure During Spinal Anesthesia, *Ann. Surg.* **104**:41, 1936. (b) Burch, J. C., and Harrison, T. R.: The Effect of Spinal Anesthesia on the Cardiac Output, *Arch. Surg.* **21**:330 (Aug.) 1930; (c) The Effect of Spinal Anesthesia on Arterial Tone, *ibid.* **22**:1040 (June) 1931. (d) CoTui: Spinal Anesthesia: The Experimental Basis of Some Prevailing Clinical Practices, *ibid.* **33**:825 (Nov.) 1936. (e) Ferguson, L. K., and North, J. P.: Observations of Experimental Spinal Anesthesia, *Surg., Gynec. & Obst.* **54**:621, 1932. (f) Heymans, C.; Bouckaert, J. J., and Bert, P.: Mécanisme du collapsus circulatoire. Influences des traumatismes et de la rachianesthésie sur les réflexes circulatoires sino-carotidiens, *Compt. rend. Soc. de biol.* **112**:715, 1933. (g) Labat, G.: Regional Anesthesia, in Nelson Loose Leaf Surgery, New York, Thomas Nelson & Sons, 1931, vol. 1, pp. 533-569; Regional Anesthesia: Its Technic and Clinical Application, Philadelphia, W. B. Saunders Company, 1928, p. 525. (h) Maxson, L. H.: Spinal Anesthesia, Philadelphia, J. B. Lippincott Company, 1938. (i) Schilf, E., and Ziegner, H.: Das Wesen der Blutdrucksenkung bei der Lumbalanästhesie, *Arch. f. klin. Chir.* **130**:352, 1924. (j) SeEVERS, M. H., and Waters, R. M.: Circulatory Changes During Spinal Anesthesia, *California & West. Med.* **35**:169, 1931; (k) Respiratory and Circulatory Changes During Spinal Anesthesia, *J. A. M. A.* **99**:961 (Sept. 17) 1932. (l) Smith, G. G., and Porter, W. T.: Spinal Anesthesia in the Cat, *Am. J. Physiol.* **38**:108, 1915. (m) Steel, W. A.: Blood Pressure Maintenance in Spinal Anesthesia, *J. A. M. A.* **84**:79 (Jan. 10) 1925.

2. (a) Gray, H. T.: A Study of Spinal Anesthesia in Children and Infants, *Lancet* **2**:913 and 991, 1909. (b) Gray, H. T., and Parsons, L.: Blood Pressure Variations Associated with Lumbar Puncture, and the Induction of Spinal Anesthesia, *Quart. J. Med.* **5**:339, 1912. (c) Goldfarb, W.; Provisor, B., and Koster, H.: Circulation During Spinal Anesthesia, *Arch. Surg.* **39**:429 (Sept.) 1939. (d) Smith, H. W.; Rovenstine, E. A.; Goldring, W.; Chasis, H., and Ranges, H. A.: The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation, *J. Clin. Investigation* **18**:319-341, 1939. (e) Schubert, O. O.: On the Distribution of the Circulation in Spinal Anesthesia, *Acta chir.*

The evidence in the literature for diminished vasoconstriction is as follows:

Burch and Harrison<sup>1c</sup> showed that spinal anesthesia increases the rate of flow of perfusion fluid through the femoral and brachial arteries of dogs. They showed also that compensatory vasoconstriction following hemorrhage by bleeding as shown by a marked diminution in the perfusion rate does not occur in the animals which receive spinal anesthesia, since in these animals the perfusion rate is unchanged or increased by hemorrhage. They concluded that

. . . in subjects under spinal anesthesia, the power of active vasoconstriction is, however, more or less completely absent because of the paralysis of the vasomotor fibers.

The observations by Herrick, Essex and Baldes<sup>3</sup> that lumbar sympathectomy produces a permanently increased blood flow in the femoral artery of normal dogs and that the increased arterial flow is larger than probably can be accounted for by dilatation of the vessels of the skin and the paw were evidence of vasodilatation not only in the vessels of the skin but also in the vessels of the skeletal muscles.

Horton and Craig<sup>4</sup> presented roentgen evidence (after injection of metallic mercury through a cannula in the abdominal aorta) of vasodilatation in the arteriolar tree of the hind extremity of a dog denervated by lumbar sympathectomy.

Bradshaw,<sup>1a</sup> using cats anesthetized with barbital sodium, showed a marked fall in blood pressure during spinal anesthesia and an absence of such a fall during spinal anesthesia in cats subjected to sympathectomy ten days previously.

Shaw, Steele and Lamb<sup>5</sup> found that the arteriovenous blood oxygen difference during spinal anesthesia is invariably increased because of

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Scandinav. (supp. 48) **78**:1, 1936. (f) Polano, H.: Experimentelle Untersuchungen über das Verhalten des Minutenvolumens des menschlichen Herzens bei Äthernarkose, Lumbalanaesthesie und nach operativen Eingriffen, Deutsche Ztschr. f. Chir. **239**:505, 1933. (g) Burch and Harrison.<sup>1b</sup>

3. Herrick, J. F.; Essex, H. E., and Baldes, E. J.: Observations on the Blood Flow in the Femoral Artery in the Dog Eight to Thirty-Four Months Following Lumbar Sympathectomy, Proc. Staff Meet., Mayo Clin. **7**:711, 1932; The Effect of Lumbar Sympathectomy on the Flow of Blood in the Femoral Artery of the Dog, Am. J. Physiol. **101**:213, 1932.

4. Horton, B. T., and Craig, W. M.: Evidence Shown in Roentgenograms of Changes in the Vascular Tree Following Experimental Sympathetic Ganglionectomy, Arch. Surg. **21**:698 (Oct.) 1930.

5. Shaw, J. L.; Steele, B. F., and Lamb, C. A.: Effect of Anesthesia on the Blood Oxygen: I. A Study of the Effect of Ether Anesthesia on the Oxygen in the Arterial and in the Venous Blood, Arch. Surg. **35**:1 (July) 1937.



the fall of the oxygen content of the venous blood (during spinal anesthesia). Presupposing vasodilatation as the cause of the blood pressure fall which they also observed, they assumed in order to explain the increased arteriovenous oxygen difference that arteriolar dilatation causes the blood to stagnate in the anesthetized region.

Freeman and associates,<sup>6</sup> using procaine hydrochloride locally to prevent pain, showed that in the sympathectomized dog the blood flow varies directly with the blood pressure, while in the normal dog with intact vasomotor system, wide variations in flow are encountered as the blood pressure is being reduced. In general as the pressure is reduced in both, the flow is greater in the sympathectomized animal. They noted also that normal dogs are able to tolerate a greater blood loss than sympathectomized dogs and that the former show less fall in blood pressure. This they attributed to the ability of the normal dogs to constrict the arteriolar bed.

The basis presented in the literature for the belief that hypotension is due to diminished cardiac output is as follows:

Gray <sup>2a</sup> and Gray and Parsons <sup>2b</sup> concluded that the preliminary fall is due to an increased capacity of the veins, the capillaries and the arteries resulting from flaccidity of the abdominal and skeletal muscles and that the main fall results from thoracic paralysis and therefore loss of aspiratory action of the thorax and consequent diminished cardiac output.

Burch and Harrison <sup>1b</sup> in 10 observations on 8 dogs reported a fall of cardiac output following spinal anesthesia. The average decrease in cardiac output was 23 per cent, and the average decrease in blood pressure in the same experiments was 44 per cent. They observed that the fall in blood pressure preceded that in cardiac output.

Polano <sup>2f</sup> reported equivocal results after observations on 7 patients under spinal anesthesia, 5 showing no change in cardiac output and 2 showing a decrease. In none of these cases was there any marked drop in blood pressure.

Schuberth <sup>2e</sup> reported on the cardiac output in 14 subjects under spinal anesthesia. He found that in 4 the cardiac output increased. In 2 of these the systolic pressure increased; in 1 it remained unchanged, and in the fourth it fell 25 mm., from 155 to 130. In the remaining 10 subjects the cardiac output fell, the most marked reduction being associated with the greatest fall of pressure.

Provisor, Goldfarb and I <sup>2c</sup> found a consistent fall in the cardiac output of approximately 33 per cent by the gasometric method.

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6. Freeman, N. E.; Shaffer, S. A.; Schechter, A. E., and Holling, H. E.: The Effect of Total Sympathectomy on the Occurrence of Shock from Hemorrhage, *J. Clin. Investigation* 17:359, 1938.

Smith and associates<sup>21</sup> reaffirmed the opinion of Gray and Gray and Parsons on the basis of blood pressure observations in 18 anesthetized patients not subjected to operation. They stated:

. . . The fact that the diastolic pressure may not fall at all, that it rarely falls below 60 mm., and that it invariably falls less than the systolic pressure, is directly opposed to the changes to be expected during arteriolar dilatation.

The experience with spinal anesthesia on which the present study is based is far in excess of 20,000 cases. During the first 2,000 of these cases blood pressure records were kept carefully, and the impression was that it was impossible to predict with any degree of accuracy in any given case what would happen to the pressure after the injection. In some instances there was no appreciable change; in others there was a maximum fall of 8 or 10 mm. of mercury. In a fairly large number there was a drop of 20 to 30 mm. within ten minutes of the time of injection, and this fall was sustained for approximately three quarters of an hour, the return to normal immediately preceding the return of sensation. In some the pressure fell 50 to 75 mm. within ten minutes after anesthesia was induced and within another ten minutes would be back to within 20 mm. of the normal. In a small number the pressure would drop within ten minutes to such a level that no regular pulse could be felt nor could the pressure be ascertained by the sphygmomanometer. In all of these cases there was generally a correspondence between the systolic and diastolic changes. It is true that all of these patients were anesthetized in preparation for operation and that a great many of the observations on blood pressure were made during the operation. But there were enough patients who were observed after anesthetization and while waiting for the surgeon to finish operating on another patient to suggest strongly that in the main operative procedure is not essential to the blood pressure drop noted during spinal anesthesia. However, it was deemed advisable to make a serious study of the blood pressure changes found after spinal anesthesia in human beings without the interfering factor of the operative procedure.

The blood pressure in patients not subjected to operation was studied before and during spinal anesthesia under three sets of conditions.

#### METHOD

An observer specially trained to read the blood pressure was assigned 1 case in the operative schedule each morning. All observations before operation were made in a small anteroom. The patients were studied in three groups.

*Group 1.*—Sixty-five patients were studied for a control period of at least twenty minutes, systolic and diastolic blood pressure readings being taken every two minutes. Then 150 mg. of procaine hydrochloride dissolved in 4 cc. of cerebrospinal fluid was injected into the subarachnoid space between the second and third lumbar vertebrae. The anesthetic was given with the patient in the

lateral prone position, and the patient was immediately placed in the dorsal position and the table tilted to an 8 to 10 degree Trendelenburg angle. The anesthesia was induced in all patients in the same manner. Blood pressure readings at two minute intervals were immediately resumed and continued for another period of at least twenty minutes. Subsequently the patients were operated on.

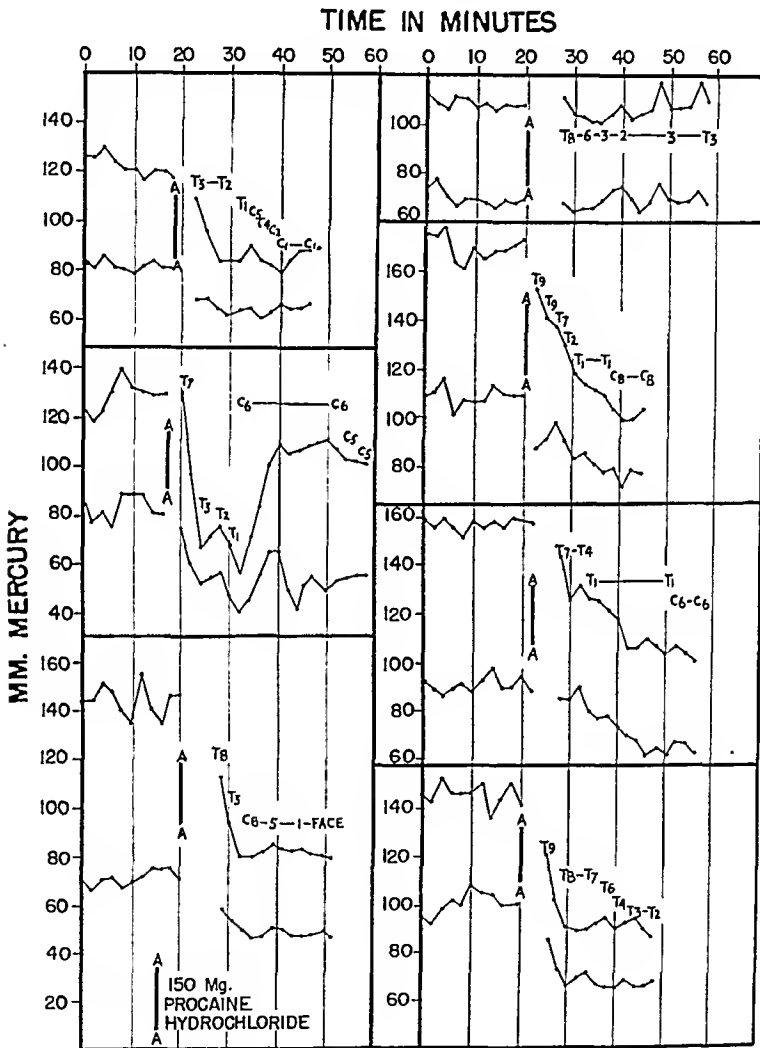


Chart 1.—Examples of the type of blood pressure response to spinal anesthesia observed in 65 patients not subjected to operation. When the systolic pressure falls, there is a corresponding percentage fall in diastolic pressure. In this and in charts 2 and 3 the levels of anesthesia are denoted by labels of the cord levels which correspond to the involved dermatomes (T, thoracic; C, cervical; A, anesthesia).

Group 2.—Control blood pressure levels were obtained in 4 patients. The lower extremities were then bandaged with elastic bandages from the toes to the groin to support and compress the venous return in the manner used in treating varicose

veins. New blood pressure base lines were then obtained; spinal anesthesia was induced as in group 1; the patients were placed in an 8 to 10 degree Trendelenburg position, and the blood pressure studies were continued.

*Group 3.*—Six patients were studied as in group 1, except that before the readings were begun and throughout the entire period they were kept in a 45 degree Trendelenburg position.

## RESULTS

*Group 1.*—Most patients show a fall in blood pressure during spinal anesthesia. A small number, however, do not. In those in whom hypotension develops there is no way of accurately predicting the degree of

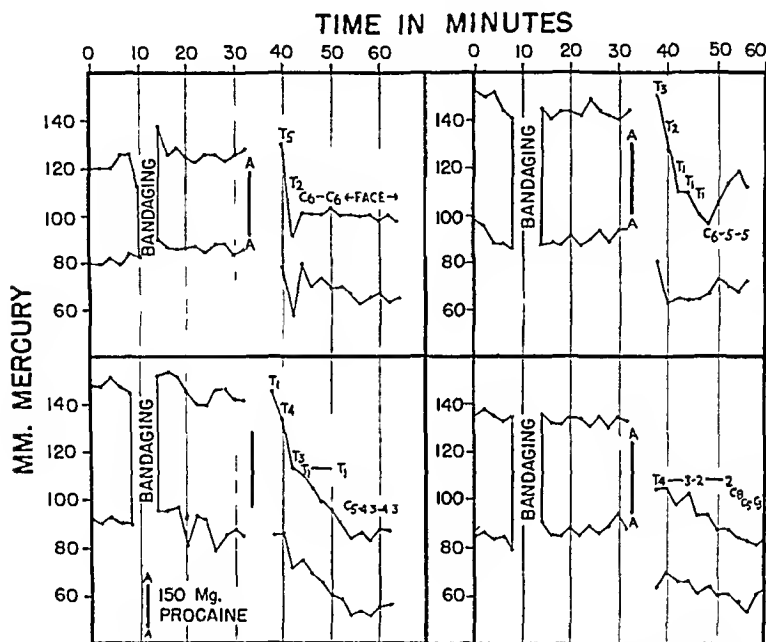


Chart 2.—Effect on the hypotension of spinal anesthesia of bandaging the lower extremities in the attempt to prevent pooling in them. Bandaging does not inhibit the expected fall of blood pressure.

fall. When the systolic pressure falls, there is a corresponding percentage fall in the diastolic pressure and a fall in the pulse pressure. The individual curves vary considerably. Chart 1 is a good example of the types of blood pressure response. After hypotension develops the level of both systolic and diastolic pressures is not even but is fluctuating. However, there is a striking tendency toward parallelism, even in the undulations, which suggests a dependence on the same causes. The degree of fall does not necessarily correspond with the level of anesthesia. This conclusion corroborates the findings of Bradshaw.<sup>1a</sup> It should be noted here also that even the control levels are undulating and not flat.

The hypotension disappears as the anesthesia wears off, and in these cases this occurred after fifty and sixty minutes of anesthesia. While the levels of anesthesia have been determined by the response to pinprick and have been denoted by labels of the cord levels which correspond to the involved dermatomes, attention must be called to the fact that

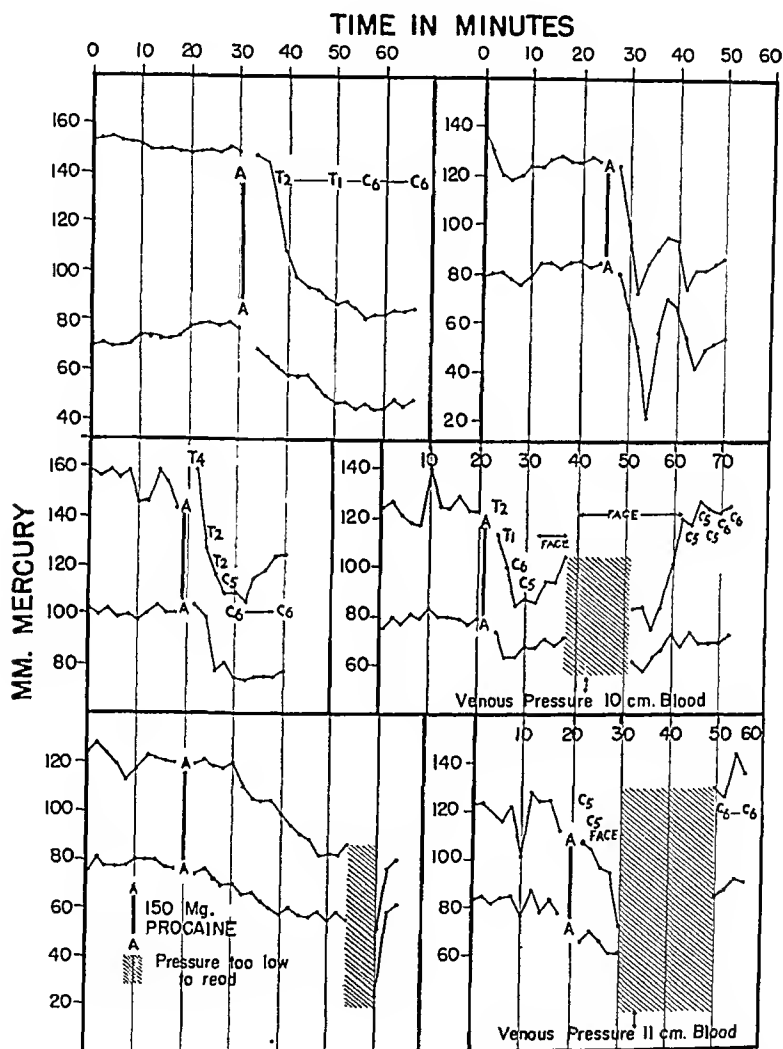


Chart 3.—Effect on the hypotension of spinal anesthesia of a 45 degree Trendelenburg posture, which prevents venous pooling in the lower extremities and abdomen. The position does not inhibit the expected fall of blood pressure.

there may be a marked difference between the reaction to a pinprick and to scalpel incision. On many occasions in the 20,000 odd experiences on which this study is based, patients were tested by pinprick on the abdomen after receiving a subarachnoid injection of 150 mg. of procaine hydrochloride and were considered adequately anesthetized for lapar-

otomy, yet they screamed with pain when the scalpel cut through the skin. However, all patients in this study still had enough anesthesia to permit performance of abdominal operations on them after the blood pressure study was completed.

*Group 2.*—There was no significant difference in the blood pressure fall (chart 2).

*Group 3.*—There was no inhibition of the blood pressure fall. The hypotension was extreme in some cases (chart 3).

#### COMMENT

It has been shown that when there is a fall in systolic pressure during spinal anesthesia there is also a roughly corresponding percentage fall

*Calculated Percentage Fall of Systolic and Corresponding Diastolic Pressure During Spinal Anesthesia in Eighteen Cases\**

Case	Blood Pressure Before Anesthesia		Blood Pressure During Anesthesia		Percentage Fall During Anesthesia	
	Systolic	Diastolic	When Systolic Fell to	Diastolic Was	Systolic	Diastolic
1.....	120	80	90	62	25	22
2.....	140	90	108	70	23	22
3.....	140	90	120	90	14	0
4.....	140	80	105	50	25	38
5.....	140	90	100	48	29	43
6.....	135	90	95	65	40	28
7.....	120	85	90	60	25	30
8.....	90	70	60	35	33	50
9.....	120	90	90	70	25	22
10.....	115	60	85	50	26	17
11.....	120	65	100	50	17	23
12.....	140	80	120	80	15	0
13.....	120	80	90	60	25	25
14.....	120	78	98	60	18	26
15.....	150	100	90	60	40	40
16.....	140	100	110	70	21	30
17.....	110	80	70	40	36	50
18.....	140	80	110	50	21	37

\* Taken from points in eighteen graphs published by Smith, Rovenstine, Goldring, Chasis and Ranges.

in diastolic pressure. Since diastolic pressure is a measure of peripheral arteriolar resistance, these observations were consistent with the theory that the hypotension of spinal anesthesia is due, in part at least, to arteriolar dilatation resulting from an interruption of vasopressor impulses in the anesthetic-bathed roots of the cord.

The changes in pressure observed during spinal anesthesia were different from those claimed by Smith and associates, who found insignificant diastolic changes. This becomes more difficult to understand when their graphs are examined. In 16 of their 18 cases there was a definite fall in diastolic pressure. In more than half of their cases (cases 4, 5, 7, 8, 11, 13, 14, 15, 16, 17 and 18), there were points at which the percentage fall of diastolic pressure was as great or greater than that of the systolic pressure. The table shows the actual change and the calcu-

lated percentage drop of systolic as against diastolic pressure at corresponding points taken from their eighteen graphs. Statistical analysis of the data in this table yields a probability value of 0.4839, which means that there was no significant difference between the falls in systolic as against diastolic pressures in their cases.

If the fall in blood pressure during spinal anesthesia is due to venous pooling in the deep veins of the lower extremities on failure to receive support from the now paralyzed skeletal muscles, as Smith and associates claimed, it should be possible to inhibit this pooling by the preliminary application of elastic bandages to the extremities to compress the veins in much the same way as elastic bandages are used to prevent pooling of blood in varicose veins. Figure 2 shows the results of such trials, and apparently the regularly expected fall cannot be so inhibited.

Weiss, Wilkens and Haynes,<sup>7</sup> studying the effect of small doses of sodium nitrite in normal subjects, noted that there were no symptoms or only slight symptoms of circulatory changes with the subjects in the prone position but that if the subjects were tilted on the table to an angle of 75 degrees with the head up there were signs of progressive vasomotor collapse often terminating in syncope. A return to the prone position was followed by immediate recovery of normal blood pressure. By varying the dose of sodium nitrite and the angle of tilting the body the duration as well as the degree of circulatory collapse could be regulated. The authors pointed out that the fall in venous pressure and the resulting decreased return of venous blood to the heart in the upright position must be due to a pooling of an appreciable amount of blood in the venous portion of the vascular bed. They found that sodium nitrite decreases the tone of the veins of the hand as indicated by the decrease in resistance of these vessels to graded pressure. If, therefore, instead of the subject being raised to the upright position he was tilted to the Trendelenburg position, venous stasis in the lower extremities and the abdomen could not occur because of gravity drainage toward the heart. This mechanism for the development of hypotension is similar to that conceived by Smith and associates to occur during spinal anesthesia, and it seems that the extreme Trendelenburg position should inhibit the development of the hypotension during spinal anesthesia also. The blood could no longer remain pooled in the supposedly unsupported and dilated veins in the paralyzed skeletal muscles or the dilated abdominal veins because gravity would drain it out of them. And even if the aspiratory action of the thorax were abolished by the supposed thoracic paralysis described by

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7. Weiss, S.; Wilkens, R. W., and Haynes, F. W.: The Role of the Venous System in Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* 16:85, 1937.

Gray and Parsons,<sup>2b</sup> blood would not remain in dilated veins of the abdomen, because gravity would drain it into the thorax.

Chart 3 shows the results of such trials in 6 cases, and it is evident not only that the fall in blood pressure was not inhibited but that maximal falls were obtained in some of these cases. In 2 instances in which the fall was so great that manometric readings were not obtainable, the venous pressure read by the direct method <sup>8</sup> was 10 and 11 cm. of blood, respectively. The anesthesia did not involve any higher levels than in the group of 44 cases, and in no instance was there paralysis of the muscles of the shoulder girdle, including the pectoral muscles, or of the arm.

It seems from these experiments with 10 human beings that the hypotension of spinal anesthesia is not seriously dependent for its development on the pooling of blood in unsupported dilated veins lying in paralyzed skeletal muscles or within the abdomen.

#### CONCLUSIONS

There is approximately the same percentage drop in systolic and diastolic blood pressures during spinal anesthesia in patients not subjected to operation. This is in accord with what would be expected if decreased arteriolar constriction followed the induction of spinal anesthesia.

The development of hypotension following the induction of spinal anesthesia in patients with the extremities supported by elastic bandages or in the extreme Trendelenburg position is evidence against venodilatation as the causative factor of the blood pressure fall.

The decreased pulse pressure indicates a decrease in cardiac output. Decreased cardiac output is a factor but probably not the only one responsible for the hypotension of spinal anesthesia.

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8. Moritz, F., and von Tabora, D.: Ueber ein Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* 89:475, 1910.



# AFFERENT CONDUCTION FROM EXTREMITIES THROUGH DORSAL ROOT FIBERS VIA SYMPATHETIC TRUNKS

RELATION TO PAIN IN PARALYZED EXTREMITIES

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In an experimental anatomic investigation carried out on cats and dogs, Kuntz and Farnsworth<sup>1</sup> demonstrated nerve fibers of spinal ganglion origin in the gray communicating rami which join the nerves which supply the upper and lower extremities. These fibers are afferent components of the spinal nerves through the ventral roots of which the preganglionic fibers involved in the sympathetic innervation of the extremities reach the sympathetic trunk ganglions. Those which traverse the gray communicating rami which join the nerves to the upper extremity, therefore, are afferent components of the upper thoracic nerves, probably including the first to the fifth. Those which traverse the gray communicating rami which join the nerves to the lower extremity are afferent components of the lower thoracic and first and second lumbar nerves. These afferent fibers, like the preganglionic sympathetic components of the same nerves, enter the sympathetic trunk via the corresponding white communicating rami. Those which traverse the gray communicating rami which join the nerves to the upper extremity ascend in the sympathetic trunk from the segments in which they join it to the levels at which the gray rami in question arise. Those which traverse the gray communicating rami which join the nerves to the lower extremity descend in the sympathetic trunk from the segments in which they join it to the levels at which the gray rami which they enter respectively arise.

The data advanced by Kuntz and Farnsworth indicate the occurrence of afferent nerve fibers in the gray communicating rami only in relatively small numbers, but in sufficient numbers to be functionally significant. The peripheral distribution of these fibers in the extremities

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From the St. Louis University School of Medicine.

1. Kuntz, A., and Farnsworth, D. I.: Distribution of Afferent Fibers via the Sympathetic Trunks and Gray Communicating Rami to the Brachial and Lumbosacral Plexuses, *J. Comp. Neurol.* **53**:389-399 (Dec.) 1931.

has not been determined. They probably terminate mainly in relation to the blood vessels.

Attempts to elicit pain in experimental animals by stimulation of receptors in an extremity which had been deprived of all afferent fibers of spinal ganglion origin except those which enter it via the sympathetic trunk and the communicating rami have yielded only negative results. The fibers in question obviously do not belong to the category of peripheral afferent conductors which normally conduct impulses of pain. The present investigation has been undertaken to determine whether reflex or other recognizable responses can be elicited by appropriate stimulation of these fibers. This would prove their functional potency as afferent conductors.

#### METHODS

Cats were used as the experimental animals. The operative procedures were carried out with the animals under anesthesia induced with soluble pentobarbital. In one series, the spinal cord was transected between the levels of the roots of the second and third lumbar nerves or just caudal to this level. If the section occurred caudal to the third lumbar nerves, the roots of the latter were interrupted in order to prevent afferent conduction through them. The portion of the spinal cord caudal to the section was destroyed in order to prevent segmental and crossed reflexes through it. The sympathetic trunk was interrupted unilaterally below the second lumbar communicating rami by extirpation of several segments. In another series, the roots of the spinal nerves from the fourth cervical to the first or second thoracic inclusive were cut unilaterally within the vertebral canal in order to insure interruption of all afferent fibers to the forelimb except those of the second or third and lower thoracic nerves which enter it via the sympathetic trunk and communicating rami.

Various means of stimulation, particularly pressure and the faradic current, were applied to the lower extremities in the first series and to the upper extremity on the side on which the nerves had been interrupted in the second. Particular attention was given to reflex responses of the iris and the vibrissae on the upper lip. Most of the stimulation experiments were carried out one hour or longer after operation but while the animal remained under surgical anesthesia. In some instances they were repeated while the animal was in the waking state.

#### RESULTS

After the animals had recovered from the anesthesia, following transection of the spinal cord at the lumbar level indicated, the lower extremities were insensitive to the exteroceptive and proprioceptive stimuli ordinarily used in sensory tests. After section of the roots of the lower five cervical and the first thoracic nerves, the corresponding upper extremity also was insensitive to the same stimuli. The voluntary muscles of the upper extremity also were completely paralyzed. Stimulation of the distal segment of the ventral root of the second thoracic

nerve in the animals in which this nerve was interrupted elicited no motor responses in the extremity. Postmortem examination revealed no direct fiber connections between the second and first thoracic nerves in any of the animals in which the experiments involved the upper extremity.

After transection of the spinal cord between the levels of the roots of the second and third lumbar nerves, squeezing of the leg or the thigh, tightening of a tourniquet either below or above the knee or strong faradic stimulation over the femoral or the sciatic nerve on the side on which the sympathetic trunk remained intact frequently resulted in dilation of both pupils in some degree, particularly if they were somewhat constricted at the beginning of stimulation. This response was elicited repeatedly in the same animals while they were under anesthesia and in some of them also while they were in the waking state. The width of the pupil usually was increased 1 to 2 mm. and in some instances over 2 mm. The same stimuli applied to the lower extremity on the side on which the sympathetic trunk was interrupted in the lumbar segments resulted in no change in the width of the pupils.



Fig. 1.—Photographs taken with a flash bulb camera at distance of 3 inches (7.6 cm.), with aperture of F16, showing extent of dilation of the pupil in response to stimulation of the forelimb following section of both roots of the lower five cervical and the first thoracic spinal nerves. *A*, before stimulation; *B*, during stimulation by means of tourniquet on arm (cat 7); *C*, before stimulation; *D*, during strong faradic stimulation of arm (cat 16).

After section of the roots of the fourth cervical to the first thoracic nerve inclusive, squeezing the limb, tightening a tourniquet either below or above the elbow or strong faradic stimulation elicited greater dilation of the pupils than the same stimuli applied to the lower extremity following transection of the spinal cord between the second and third lumbar nerve roots (fig. 1). Faradic stimulation of the forelimb also elicited a reflex response in the upper lip, particularly on the contralateral side, characterized by sudden movements of the vibrissae. This reaction was observed repeatedly, but only in response to faradic stimulation.

The same reflex responses were elicited by stimulation of the forelimb in the animals in which the roots of the second thoracic nerve were divided in addition to those of the lower five cervical and the first thoracic, but less constantly. The reactions also were less marked.

During the stimulation experiments carried out while the animals were in the waking state, mild sensory reactions were observed in some instances. This occurred both during stimulation of the lower extremity following transection of the spinal cord and during stimulation of the upper extremity following section of the roots of the lower five cervical and the first or first and second thoracic nerves.

#### COMMENT

The experimental results obtained in this investigation support the assumption that afferent nerve impulses of certain functional categories may be conducted into the spinal cord from an extremity deprived of all the afferent components of the nerves through which it receives its voluntary efferent innervation. Since it has been demonstrated anatomically that afferent components of the spinal nerves adjacent to those through which the extremity receives its voluntary innervation reach it via the sympathetic trunk and communicating rami, it seems most probable that the afferent conduction in question is accomplished through these fibers. The pupillary responses to stimulation of either a lower or an upper extremity with no other afferent fibers remaining functionally intact undoubtedly represent reflex reactions carried out through the spinal cord and the sympathetic innervation of the iris. The reflex movements of the vibrissae on the upper lip elicited by faradic stimulation of the upper extremity deprived of all its afferent innervation except the fibers of spinal ganglion origin which reach it via the sympathetic trunk and communicating rami from segments lower than the first or second thoracic also are carried out through the spinal cord and efferent conduction pathways to the lip. The latter undoubtedly involve efferent components of the facial nerve, since the reaction includes contraction of muscles of the lip and is not abolished by section of the cervical sympathetic trunk on the corresponding side. It is not inconceivable that stimulation of the afferent fibers in question, under the conditions of our experiments, might elicit reflex responses through somatic motor fibers, but no unmistakable evidence of such responses has been obtained.

It is conceivable that sympathin liberated as a result of stimulation of the sympathetic fibers in the extremity might have played a role in the reactions of the iris described. This is precluded in the experiments in which stimulation was effected by tightening a tourniquet on the limb, since circulation in the distal part of the limb was arrested for the duration of the stimulation. The responses of the iris and the vibrissae as well as the mild sensory reactions observed in the experiments carried out while the animals were in the waking state can be explained most satisfactorily on the assumption that afferent impulses

actually were conducted from the extremities into the spinal cord. Upward conduction in the spinal cord probably was accomplished through the fasciculus proprius system. It obviously involved crossed as well as uncrossed pathways, since the pupillary responses to unilateral stimulation were bilateral and the reactions of the vibrissae were most marked on the contralateral side.

Certain reported clinical observations have a significant bearing on the problem of afferent conduction from the extremities via the sympathetic trunks. Slaughter<sup>2</sup> reported the case of a man 31 years of age with complete transection of the spinal cord at the level of the first

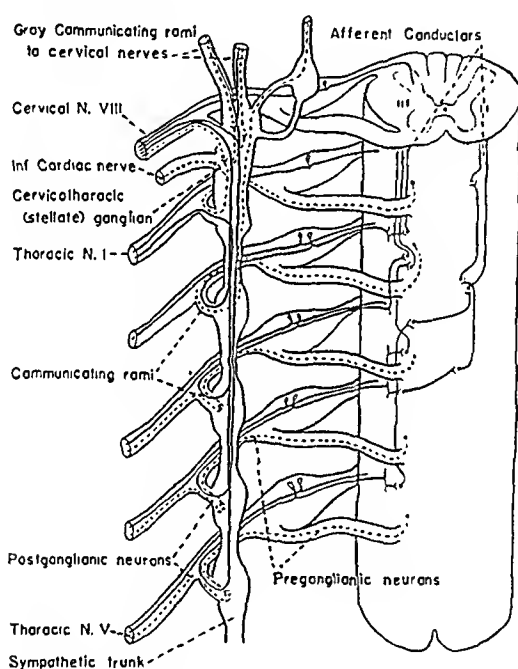


Fig. 2.—Diagram illustrating the probable anatomic relations of afferent components of the thoracic nerves below the second in man which reach the upper extremity via the sympathetic trunk and communicating rami.

lumbar vertebra. The lower extremities were completely paralyzed and insensitive to the usual exteroceptive and proprioceptive stimuli. This patient suffered severe burning, prickling pains in the legs, which subsided following bilateral extirpation of the lumbar segments of the sympathetic trunk and section of the hypogastric nerves. Since the pain in the legs was relieved by sympathectomy, Slaughter assumed that the impulses in question were conducted into the spinal cord via the sympathetic trunks. He further postulated conduction in short

2. Slaughter, R. F.: Relief of Causalgic-Like Pain in Isolated Extremity by Sympathectomy: Case Report, *J. M. A. Georgia* **27**:253-256 (July) 1938.

relays in the sympathetic trunk. Hyndman and Wolkin<sup>3</sup> reported 2 cases with paralysis of both lower extremities and complete anesthesia to all tests for exteroceptive and proprioceptive sensibility up to the middle level of the thigh, caused by fracture of the second lumbar vertebra, in which certain varieties of sensation referable to the feet could be elicited by appropriate stimulation. Patency of the sympathetic

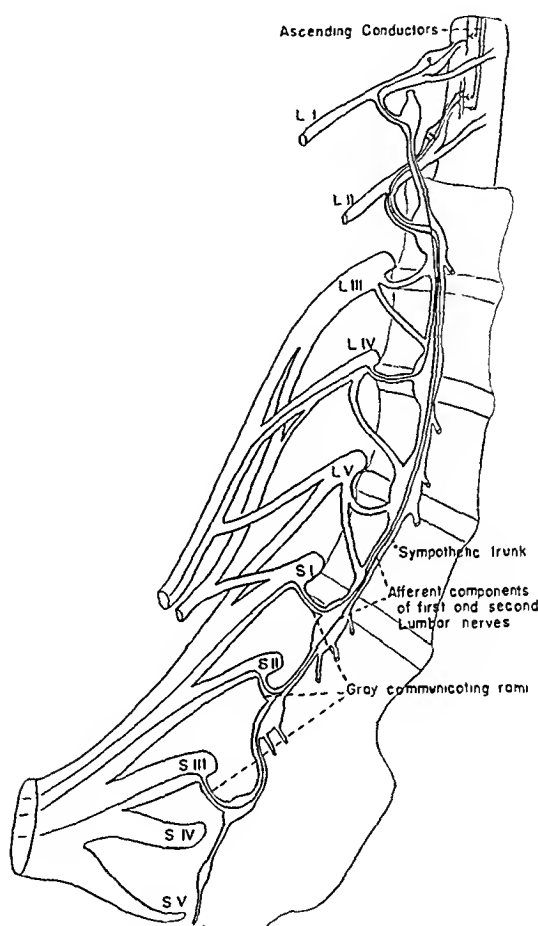


Fig. 3.—Diagram illustrating the probable anatomic relations of afferent components of the first and second lumbar nerves in man which reach the lower extremity via the sympathetic trunk and communicating rami.

innervation of the lower extremities in these patients was demonstrated by thermoregulatory and sweating tests. One of these patients, a man 30 years of age, stated that while lying quietly he could feel pulsations

3. Hyndman, O. R., and Wolkin, J.: The Sympathetic Nervous System: Influence on Sensibility to Heat and Cold and Certain Types of Pain, *Arch. Neurol. & Psychiat.* **46**:1006-1016 (Dec.) 1941.

in his feet which were synchronous with his cardiac rhythm. Inflation of a blood pressure cuff, placed just above the knee, sufficient to collapse the arteries resulted in marked tingling in the foot. The other patient, a man 28 years of age, experienced a tingling sensation and aching in the foot twenty seconds after it was immersed in ice water. In an attempt to explain these phenomena, Hyndman and Wolkin postulated the existence of afferent sympathetic fibers or antidromic conduction in efferent sympathetic fibers.

In view of the anatomic demonstration that afferent components of spinal nerves other than the ones through which the extremity receives its voluntary innervation enter it via the sympathetic trunk and communicating rami and the experimental data reported in the present paper, sensory phenomena in patients with paralyzed lower extremities due to spinal cord injury, such as those reported in the patients already referred to, probably can be explained most satisfactorily on the assumption that the afferent impulses are conducted into the spinal cord through afferent spinal nerve components which traverse the sympathetic trunk and communicating rami. The probable anatomic relations of these peripheral afferent conductors in man are illustrated diagrammatically in figure 2 for the upper extremity and figure 3 for the lower extremity. These clinical observations also afford additional evidence of the functional significance of the afferent fibers which reach the extremities via the sympathetic trunks and support the assumption that they are related mainly to the blood vessels.

#### SUMMARY

Stimulation of a lower extremity by means of pressure, tightening of a tourniquet below or above the knee or a strong faradic current in cats with the spinal cord transected between the levels of the roots of the second and third lumbar nerves elicited reflex dilation of both pupils. This reaction was abolished by interruption of the sympathetic trunk below the second lumbar segment.

The same stimuli applied to the forelimb in cats with the roots of the lower five cervical and the first or the first and second thoracic nerves cut elicited reflex dilation of both pupils and movements of the vibrissae on the upper lip on the contralateral side.

These reactions produced experimentally are regarded as evidence of conduction from the extremities into the spinal cord through afferent components of spinal nerves, other than those through which the extremities receive their voluntary innervation, which traverse the sympathetic trunks and communicating rami. The significance of afferent conduction through these fibers in certain clinical cases is suggested.

# CARCINOID TUMOR OF THE APPENDIX

REPORT OF A CASE IN WHICH EXTENSIVE INTRA-ABDOMINAL  
METASTASES OCCURRED, INCLUDING INVOLVEMENT  
OF THE RIGHT OVARY

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Review of the literature reveals that whereas carcinoid tumors of the stomach, the small intestine and the colon frequently are classed as being malignant, tumors of an exactly similar nature occurring in the appendix are regarded as being essentially benign. However, recorded instances of no less than 16 metastasizing appendical carcinoids bear witness to the fact that these seemingly innocent neoplasms are capable of widespread dissemination (table). In presenting the following report, we wish to call attention to the manifest malignancy exhibited by the tumor. In addition, the extensive metastatic involvement of the right ovary represents a complication not demonstrated by any other case which we could verify in the literature.

## REPORT OF CASE

*Clinical Aspects.*—A married white woman 47 years old registered at the Mayo Clinic on Feb. 18, 1942, complaining of weakness, hematuria and pain in the back of five years' duration.

The familial history was essentially irrelevant. The patient had been married twice and had had one child by each husband. Previously, she had had scarlet fever, typhoid fever and malaria as a child, influenza at the age of 22 years and streptococcic sore throat of recent date. Previous operations included exploratory laparotomy performed when she was 26 years old and right nephrectomy for tumor in 1936, during the period of her last postpartal convalescence.

Her complaint at the time we saw her was backache in the low lumbar region of five years' duration. The pain was never severe but was more or less constant and dragging in character without extension. It was relieved by rest and exaggerated by activity. Stiffness had not been noted. Hematuria had been a sign for a short time prior to the operation of nephrectomy previously mentioned. The

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sign had persisted intermittently since that time with mild attacks lasting about a week, usually accompanied by moderate frequency of urination. The last attack had occurred in August 1941.

In the year prior to her registration at the clinic, the patient had experienced undue weakness and a sense of fatigue. Her appetite, however, had remained good; the passage of stools had been regular, and there had been no noticeable loss of weight.

Physical examination revealed a fairly well nourished adult white woman who did not appear to be seriously ill. The skin was dry, and the mucous membranes were somewhat pale. Some asymmetry was noted in the neck; the right side was larger than the left. This did not appear to be the result of lymphadenopathy. Results of examination of the heart, the lungs and the extremities were negative.

The essential positive observations were limited to the lower part of the abdomen, in which palpation revealed a sense of resistance, especially on the right side, where tenderness was elicited on pressure. There was questionable dullness to percussion below the umbilicus. Bimanual pelvic and abdominal examination disclosed a tender mass in the right adnexal region. This mass was not freely movable and could not be separated from the body of the uterus, which with the cervix was displaced to the left. Rectal examination disclosed no intrinsic disease but confirmed the presence of a semifixed tumor in the pelvis.

Cystoscopic examination revealed granular urethritis and cystitis of moderate degree. Pyuria and bacilluria were present. Retrograde urograms revealed an essentially normal left kidney and ureter. Filling of the right ureteral stump was, however, incomplete with a filling defect which suggested pressure from without by an invasive mass.

Results of laboratory and other examinations were essentially negative, except for pyuria and bacilluria, as previously noted.

*Surgical Aspects.*—With the provisional diagnosis of malignant ovarian tumor, laparotomy was performed on Feb. 19, 1942, through a low midline incision. The appendix was adherent over the right brim of the pelvis and was the seat of a yellowish tumor approximately 3 cm. in diameter. There was also a malignant solid tumor of the right ovary which was extensively adherent to surrounding structures. The right iliac lymph nodes seemed to be grossly involved. There were, in addition, a lemon-sized cyst of the left ovary and multiple fibroids of the uterus. The operation was completed with dissection and removal of the right fallopian tube and ovary and the appendix. The left ovarian cyst was enucleated. It did not seem advisable to remove the chain of iliac lymph nodes because of the danger of tearing into the large iliac vessels to which they were densely adherent. Biopsy of one of these nodes was made for the sake of completing our pathologic diagnosis.

The patient had a comfortable convalescence and returned home on the twenty-third postoperative day after receiving a course of roentgen therapy.

*Pathologic Aspects.*—The pathologic material consisted of a specimen taken for biopsy from the pelvic peritoneum, the appendix, the right ovarian solid tumor, the left ovarian cyst and a fragment of tissue from a right iliac lymph node.

The appendix was 8 cm. long and was constricted in its proximal half. The distal half was bulbous and almost completely replaced by a yellowish tumor nodule 4 by 3 by 2 cm. On section, the muscularis propria was seen to be stretched out to form a thin capsule for the nodule. This capsule appeared to be invaded and was incomplete over half its surface, where the tissue was roughened

as a result of surgical separation, the involved part corresponding to the area from which the tissue was removed.

The right ovarian tumor was a firm, yellowish brown, poorly encapsulated mass 10 cm. in diameter with many roughened adhesions externally visible. An adherent right fallopian tube, obviously involved in the neoplastic process, was stretched out over the surface of the ovarian mass. Surfaces made by section through the tubo-ovarian nodule revealed that it was solid throughout, rather fibrous in texture and of an unusual brownish yellow color. The appearance was wholly unlike that of any ovarian neoplasm we had ever examined, and the suggestion that it might represent a metastatic carcinoid was entertained on the basis of gross examination.

The left ovarian cyst was 4 cm. in diameter and had the gross appearance of a dermoid cyst. It was filled with hair and sebaceous material but lacked a true dermoid process.

Tissue from the right iliac node was firm in texture and yellowish in color. Briefly, it appeared grossly to be metastatically involved (fig. 1).

Representative blocks of tissue were taken from the individual lesions and fixed in a 10 per cent solution of formaldehyde. These were later sectioned by the freezing method, calculated to secure a minimum of cellular distortion, and were stained routinely with hematoxylin and eosin.

Microscopic sections from the appendical tumor revealed the typical picture of carcinoid. Under the low power objective, the distinctive grouping was seen with a disposition in the form of cellular plugs or cylinders (fig. 2*a*). Here and there an alveolar arrangement was observed (fig. 2*b*), and in some areas anastomosing strands of tumor cells were noted. In between these compact units of structure were bands of fibrous tissue, varying considerably in width and in density. Sometimes the approximation of the stroma and the masses of tumor cells was intimate (fig. 3*a*); in other fields clear spaces appeared to separate the two elements (fig. 4*b*). Glands and stroma stained rather intensely with eosin. In some of the sections, remnants of the appendical lumen appeared with a few intact glands of Lieberkühn (fig. 2*a*). These glands were surrounded and in places infiltrated by masses of neoplastic cells. An occasional Kultschitzky cell was identified, but because of the advanced stage of the neoplastic process, transition zones between these cells and the tumorous elements could not be satisfactorily traced.

Under the high power objective, sections from the tumor, although cellular, appeared to consist of cells that were small and remarkably constant in size. Cytoplasm was scanty in amount and was filled with small argentaffin granules (fig. 3*b*) which stained intensely with eosin. Some of these granules stained positively for lipoid (fig. 4*a*). Cytoplasmic borders were somewhat indistinct. Nuclei were small, round and hyperchromatic, with only an occasional mitotic figure. The position of the nucleus in relation to the cytoplasm varied with the location of the cell. Toward the center of the aforementioned islands, the nuclei occupied central positions. At the periphery of these same islands, the nuclei appeared to be ranged in palisades away from the bases of the cells, which were here directed toward the supporting capsules provided by the fibrous tissue septums (fig. 3*a*). In these palisaded rows of cells, the cytoplasmic granules were most densely concentrated basally, so that each island appeared to be surrounded by a red granular rim (fig. 3*a*). In trabeculated and alveolar areas, again, this general structure was preserved, the granules in the peripheral rows of cells being

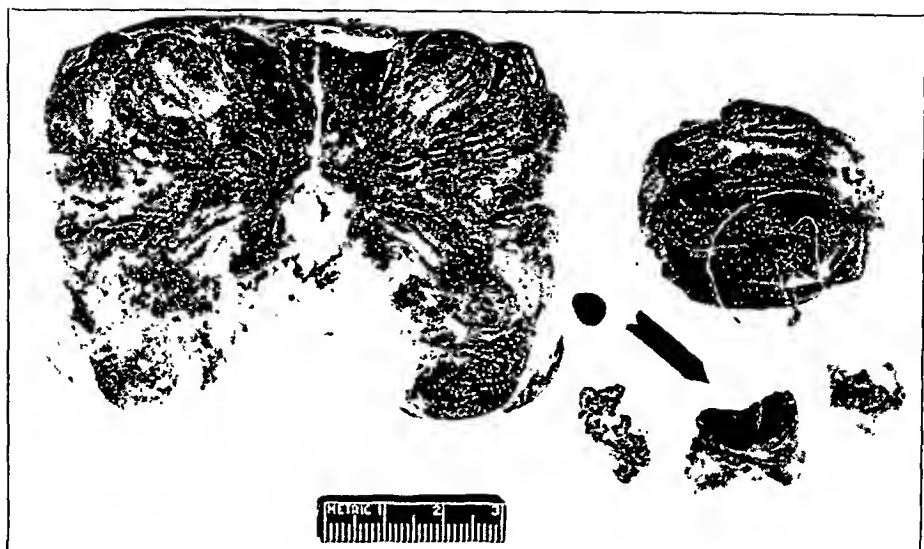


Fig. 1.—Appendical carcinoid (indicated by arrow) with extensive metastasis to the right ovary and two smaller metastatic nodules from the pelvis. Left ovarian dermoid is apparent. The small shiny object at the base of the arrow is a phlebolith from one of the pelvic veins.

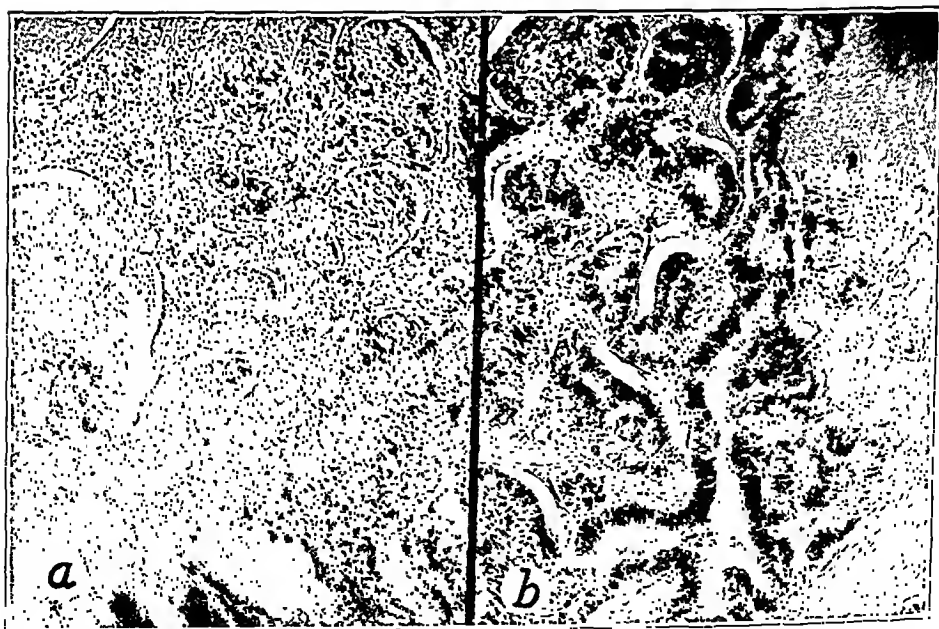


Fig. 2.—(a) Photomicrograph of carcinoid of the appendix showing characteristic disposition of small tumor cells in the form of plugs or cylinders and invasion of the crypts of Lieberkühn (hematoxylin-eosin stain;  $\times 130$ ); (b) photomicrograph of carcinoid of the appendix; in this field the tumor cells are differentiating into well formed glandular spaces (hematoxylin-eosin stain;  $\times 160$ ).

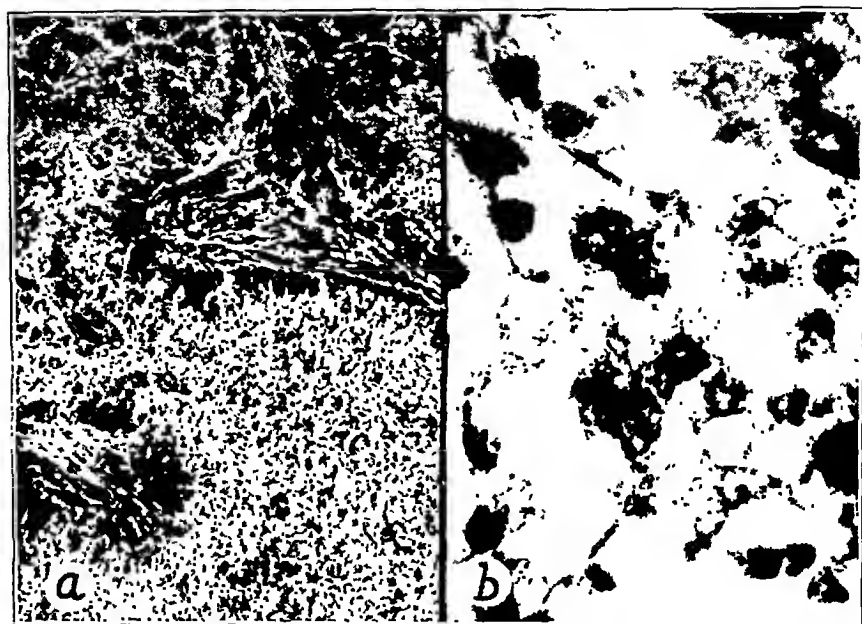


Fig. 3.—(a) Photomicrograph of carcinoid of the appendix: the section, made through the periphery of an island, shows peripheral palisading of tumor cells and rimming of cytoplasmic (dark) granules (hematoxylin-eosin stain;  $\times 350$ ); (b) photomicrograph of carcinoid of the appendix showing the argentaffin granules in the cytoplasm of the cells (silver impregnation;  $\times 800$ ).

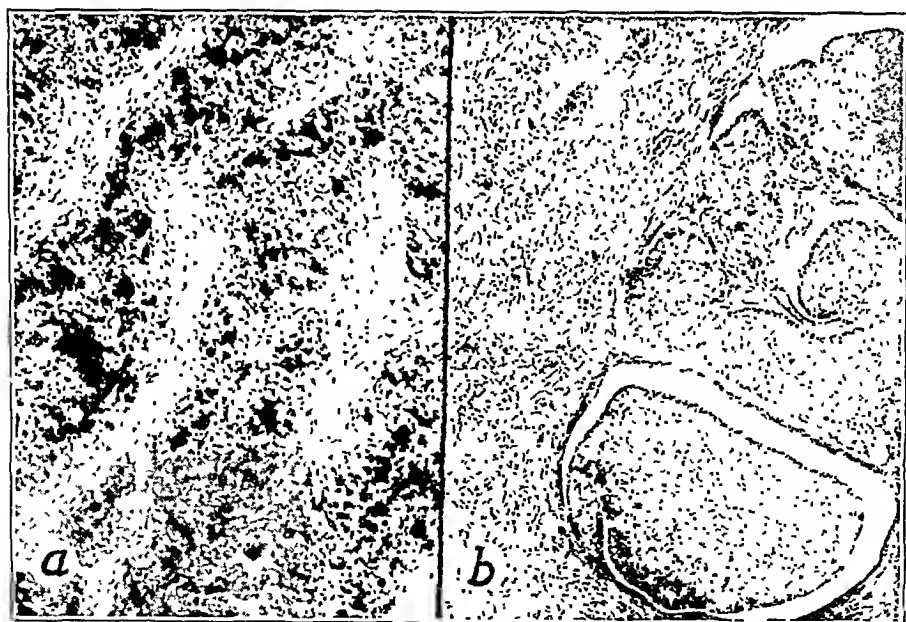


Fig. 4.—(a) Photomicrograph of carcinoid of the appendix; the dark granules represent lipoid (sudan III stain;  $\times 225$ ); (b) photomicrograph of right ovarian metastasis showing multiple plugs of tumor cells; the largest plug is separated from the fibrous stroma by a clear space (hematoxylin-eosin stain;  $\times 130$ ).

concentrated in the zone adjacent to the basement membrane. Where an alveolar pattern was present, the nuclei, again in palisades, were approximated toward the cystic lumens, with the granular cytoplasm condensed peripherally.

Cytologically, the cellular uniformity, relative lack of mitosis and differentiation into glandlike structures were typical of lesions of grade 1 of Broders' classification. (This lesion was a widely metastasizing carcinoid, and yet the microscopic pictures noted in the foregoing paragraphs could be transposed verbatim to describe most of the so-called benign examples.)

Microscopic sections taken from the right ovary and the iliac lymph node (figs. 4*b* and 5*a*) presented pictures in most details exactly similar to those described for the appendical lesion. They are illustrated in the photomicrographs. Sections

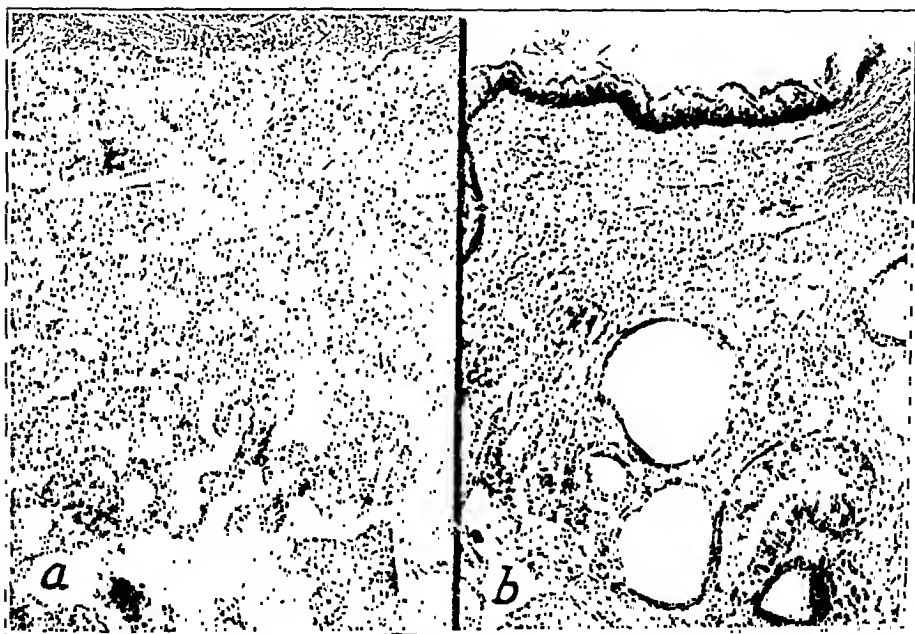


Fig. 5.—(a) Photomicrograph of iliac nodal metastasis; tumor cells are here arranged in strands, islands and pseudoacini, and the stroma is fibrous (hematoxylin-eosin stain;  $\times 60$ ); (b) photomicrograph of left ovarian dermoid, showing skin, sebaceous and apocrine glands (hematoxylin-eosin stain;  $\times 130$ ).

made from the wall of the left ovarian cyst were typical of dermoid, with a preponderance of ectodermal structures (fig. 5*b*).

#### COMMENT

*Historical Data.*—Although Oberndorfer<sup>1</sup> in 1907 first applied the term “carcinoid” to certain unusual yellowish tumors of the appendix, they had already been known for about twenty years. The neoplasm

1. Oberndorfer, S.: *Karzinoide Tumoren des Dünndarmes*, Frankfurt. Ztschr. f. Path. 1:426-432, 1907.

probably was first described by Lubarsch<sup>2</sup> in 1888. Two years later Ransom<sup>3</sup> described a malignant tumor of the ileum which is now recognized as having been carcinoid. In 1909, Burckhardt<sup>4</sup> classified carcinoids as low grade malignant tumors. Reports appeared sporadically in the literature for the next ten years. In the 1920's, the number of articles written on this subject suddenly began to increase, especially in the European literature, and Masson,<sup>5</sup> Hasegawa<sup>6</sup> and others added valuable contributions. In the past few years interest has again become aroused, and with the papers published by Jones,<sup>7</sup> Gnassi,<sup>8</sup> Wyatt,<sup>9</sup> Ariel,<sup>10</sup> Porter and Whelan,<sup>11</sup> Horsley<sup>12</sup> and many another writer, the fund of knowledge concerning the lesion has been notably augmented.

*Incidence.*—In 1939, Porter and Whelan reported a series of 84 carcinoids. They found the tumor in 0.28 per cent of surgically removed appendixes. They stated that carcinoids were twice as common in the appendix as in the small bowel and that elsewhere in the gastrointestinal tract they were found (in a decreasing order of frequency) in the stomach, the gallbladder, the duodenum, Meckel's diverticulum (if present), the cecum and the colon. In 1938, Gnassi reported 5 carcinoids of the appendix in 4,224 surgical specimens. In 1936, Jones described 6 carcinoids of the appendix; all were located in the distal portion of the appendix, and none had metastasized. He expressed the opinion that

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2. Lubarsch, O.: Ueber der primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberculose, *Virchows Arch. f. path. Anat.* **111**:280-317, 1888.

3. Ransom, W. B.: A Case of Primary Carcinoma of the Ileum, *Lancet* **2**: 1020-1023 (Nov. 15) 1890.

4. Burckhardt, J. L.: Zur Lehre der kleinen Dünndarmkarzinome, Frankfurt. *Ztschr. f. Path.* **3**:593-637, 1909.

5. Masson, P.: Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa, *Am. J. Path.* **4**:181-212 (May) 1928.

6. Hasegawa, T.: Ueber die Carcinoide des Wurmfortsatzes und des Dünndarmes, *Virchows Arch. f. path. Anat.* **244**:8-37, 1923.

7. Jones, C. B.: Argentaffin Cell Tumors: "Carcinoids" of Small Intestine and Appendix, *Am. J. Surg.* **34**:294-299 (Nov.) 1936.

8. Gnassi, A. M.: Chromargentaffin Tumors of the Appendix, *Am. J. Surg.* **40**:470-474 (May) 1938.

9. Wyatt, T. E.: Argentaffine Tumors of the Gastro-Intestinal Tract: Report of Three Cases, One with Distant Metastasis, *Ann. Surg.* **107**:260-269 (Feb.) 1938.

10. Ariel, I. M.: Argentaffin (Carcinoid) Tumors of the Small Intestine: Report of Eleven Cases and Review of the Literature, *Arch. Path.* **27**:25-52 (Jan.) 1939.

11. Porter, J. E., and Whelan, C. S.: Argentaffine Tumors: Report of Eighty-Four Cases, Three with Metastasis, *Am. J. Cancer* **36**:343-358 (July) 1939.

12. Horsley, J. S.: Cancer of Small and of Large Intestine, *Southwestern Med.* **24**:319-324 (Oct.) 1940.

they occurred five times as commonly in the appendix as in the small bowel, where according to the literature, 30 per cent were multiple. In 1940, Schuldt<sup>13</sup> reported that ordinary adenocarcinoma of the appendix had an incidence of 0.027 per cent, as compared to an incidence of 0.216 per cent for carcinoid of the appendix. We have found it to be a fairly common tumor, occurring once in about every 200 surgically removed appendixes—an incidence of 0.5 per cent. In 50 per cent of the cases, the tip of the appendix was the site of origin. Most common in the appendix, carcinoids were found in decreasing order of frequency in the ileum, the cecum, the jejunum, the colon and the stomach.

*Factors of Age and Sex.*—Carcinoids of the appendix are found among patients of various ages, including those in childhood to those in senility. Hasegawa in 1923 stated his belief that they probably began in youth and grew slowly. Jones found carcinoids most frequently among young adult persons less than the age of 35 years. Porter and Whelan observed that carcinoids of the appendix were encountered more frequently among persons in the third decade, whereas carcinoids of the small bowel were discovered later, usually among persons in the fourth or the fifth decade. No predilection according to sex has been noted in connection with these tumors.

*Origin.*—All three germ layers have been variously considered to be the source of the tumor cells or their antecedents. Probably most widely accepted now is the concept of entodermal origin. Hasegawa and Masson maintained that they arise from Kultschitzky's cells, which occur in the bases of some of the glandular crypts of Lieberkühn. According to Masson, these are argentaffin cells, since they reduce ammoniacal silver salts. They are found in all situations, ranging from the cardioesophageal junction to the rectum, and appear to be increased in number as a result of chronic inflammatory processes. This is particularly true in the appendix and in the ileum, where the incidence of origin of carcinoid tumors is highest.

In 1929, Forbus<sup>14</sup> maintained that carcinoids are endocrine tumors, and he regarded them as being distinct from carcinomas. Wyatt, in 1938, and also Gnassi, agreed with this theory. We agree with those who believe that carcinoid tumors are of glandular origin and that they are possibly derived from the argentaffin cells of the intestine.

*Malignancy.*—The question of the malignancy of these tumors has been argued pro and con for almost forty years. In 1907, Oberndorfer

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13. Schuldt, F. C.: Primary Adenocarcinoma of the Appendix and Carcinoid Tumors, *Minnesota Med.* **23**:791-795 (Nov.) 1940.

14. Forbus, W. D.: Argentaffine Tumors of the Appendix and Small Intestine, *Bull. Johns Hopkins Hosp.* **37**:130-153 (Aug.) 1925.

expressed his opinion that they are probably benign. In 1909, Burckhardt stated his belief that proliferation of the cells of this tumor was slow but that metastasis was only a question of time. Morl<sup>15</sup> suggested in 1931 that metastasis from appendiceal carcinoids was rare because the tumors generally produced symptoms early and were removed before metastasis had a chance to occur. In various reports, the incidence of invasion and metastasis in carcinoids of the small bowel is set at 20 to 25

*Cases of Metastasizing Appendical Carcinoid Reported in the Literature to 1942*

Author	Year	Site of Metastasis
Vriel <sup>10</sup> .. . . .	1909	Mesoappendix
Barth, H.: Virehows Arch. f. path Anat. 273: 63-81, 1929	1929	1 Ovary (?) * 2. Regional nodes
Cabot case 22511, New England J Med 215: 1176-1178, 1936	1936	Retroperitoneal nodes
Gubitz, W.: Virehows Arch. f. path Anat. 242: 265-274, 1923	1923	Liver and pleura
Hasegawa <sup>6</sup> .. . . .	1923	Regional nodes and liver
King, L. S. J.: J Coll Surgeons, Australasia 2: 364-384, 1930	1930	Ileocecal nodes
Knollach, J. G.: Zentralbl. f. Chir. 57: 1714-1718, 1930	1930	Mesentery
Jenis, D., and Geschlechter, C. F.: Arch Surg. 25: 16-18 (Jan.) 1934	1934	Regional nodes and liver
Mörl <sup>15</sup> . . . . .	1931	Mesentery, omentum and pleura
Oberndorfer <sup>1</sup> . . . . .	1907	Regional nodes
Phillips, E. W. M. H., and Isaak, D. H.: Brit. M. J. 1: 1127-1128, 1930	1930	Omentum
Porter and Whelan <sup>11</sup>	1939	(?) Peritoneum, mesentery, nodes, vertebral, periaxonal fat; in this case there were coexisting carcinoids of the ileum and the appendix (the former was considered to be the source of the metastasis by the authors)
Raiford <sup>16</sup> . . . . .	1933	Cecum and ileum
von Rehren, W.: Zentralbl. f. allg. Path. u. path. Anat. 36: 355-357, 1925	1925	Mesentery, peritoneum, liver and diaphragm
Steward, M. J., and Taylor, A. L.: J. Path. & Bact. 29: 136-139, 1926	1926	Pelvis
Vance, C. A.: Am. J. Surg. 24: 851-862, 1934	1934	Mesoappendix

\* On the basis of the author's photomicrographs, the tumor appears to have been an ovarian dysgerminoma with metastasis to the appendix.

per cent of the cases. When they occur in the stomach and the large intestine, almost all these tumors are deemed malignant. Clinically, the highest percentage of malignancy of carcinoids of the appendix was reported by Raiford,<sup>16</sup> his figure being 5.9 per cent. Pathologically, serosal involvement is frequently observed, but metastasis is rare. When

15. Mörl, F.: Ueber die Karzinoide des Wurmfortsatzes und des Dunndarmes, Beitr. z. klin. Chir. 153:71-86, 1931.

16. Raiford, T. S.: Carcinoid Tumors of the Gastro-Intestinal Tract (So-Called Argentaffine Tumors), Am. J. Cancer 18:803-833 (Aug.) 1933



it does occur, it is usually local in the mesenteric fat, in the regional lymph nodes and, more rarely, in the liver. The table is a list of metastasizing carcinoids recorded in the literature.

#### CONCLUSIONS

A case of metastasizing appendical carcinoma is recorded. It has been our constant observation that carcinoids, regardless of size, point of origin or presence or absence of metastasis, possess essentially the same microscopic features of cytologic differentiation and histologic structure. Origin from and differentiation into glandlike structures have been noted frequently. We therefore share with many the belief that all these tumors are adenocarcinoma of grade 1 malignancy (Broders). We do not, however, believe it would be wise to discard the designation "carcinoid" for this type of tumor. The diagnosis grade 1 adenocarcinoma (carcinoid) appears to be accurate, to designate a specific entity and to separate this entity from the ordinary type of adenocarcinoma, which is accompanied by a somewhat worse prognosis.

The Mayo Clinic.

# EXOPHTHALMIC GOITER OF THE JUVENILE TYPE

A SURVEY OF THE LITERATURE ON THE FAMILIAL ASPECTS OF THIS DISEASE AND A REPORT OF TWO ADDITIONAL CASES

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The occurrence of exophthalmic goiter in children is rather uncommon. In 1909, Sattler<sup>1</sup> reported 3,477 cases of exophthalmic goiter, in 184, or 5.3 per cent, of which the patients were children under 16 years of age. In 1933, Bram<sup>2</sup> summarized 13,000 cases of thyroid disease, in 102, or 0.8 per cent, of which the patients were children with exophthalmic goiter under the age of 11 years. Of 5,000 patients with exophthalmic goiter reported by Bram<sup>3</sup> in 1937, 128, or 2.5 per cent, were children under 12 years of age. In 1937, Crile<sup>4</sup> found only 4 patients with hyperthyroidism (0.02 per cent) under 5 years of age in a series of 26,682 patients with thyroid disease.

The causative agent responsible for exophthalmic goiter is not known. The part played by familial factors has been stressed by many authors. In 1868, Mackenzie<sup>5</sup> found this disorder in 2 sisters and in 2 children of 1 of these. Chapu<sup>6</sup> quoted Savage,<sup>7</sup> who discussed

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1. Sattler, H.: *Die Basedow'sche Krankheit im Kindesalter*, in Graefe, A., and Saemisch, E. T.: *Handbuch der gesamten Augenheilkunde*, ed. 2, Leipzig, Wilhelm Engelmann, 1909, vol. 9, pt. 2, p. 615.

2. Bram, I.: *Exophthalmic Goiter in Children of Ten and Under: One Hundred and Two Cases*, *Pennsylvania M. J.* **37**:45, 1933.

3. Bram, I.: *Exophthalmic Goiter in Children*, *Arch. Pediat.* **54**:419, 1937.

4. Crile, G., and Crile, G., Jr.: *Hyperthyroidism in Children Under Five Years of Age*, *Am. J. Surg.* **37**:389, 1937.

5. Mackenzie, M.: *Three Cases of Exophthalmic Goitre*, *Tr. Clin. Soc. London* **1**:9, 1868.

6. Chapu, A.: *De la descendance des Basedowiennes*, Thesis, Paris, no. 407, 1910.

7. Savage, G.: *Exophthalmic Goitre with Mental Disorders*, *Guy's Hosp. Rep.* **26**:31, 1883.

the familial aspects of hyperthyroidism as early as 1883. In 1884, Cantilena<sup>8</sup> reported on a family consisting of a mother, a son, a daughter and 2 children of the latter; all had exophthalmic goiter. In the same year, Oesterreicher<sup>9</sup> described the case of a woman with hyperthyroidism who gave birth to 10 children, of whom 8 (boys and girls) had exophthalmic goiter; 1 daughter had 4 children, of whom 3 showed the stigma of this disorder. In 1890, Mackenzie<sup>10</sup> reported on a family in which 8 of 10 sisters were affected; 1 of the 8 sisters had 4 children in whom also the disease developed. Thyssen,<sup>11</sup> in 1889, West,<sup>12</sup> in 1895, Sottas,<sup>13</sup> in 1896, Barret,<sup>14</sup> in 1901, Chapu,<sup>6</sup> in 1910, Brunet,<sup>15</sup> in 1919, Vallery-Radot,<sup>16</sup> in 1921, Lengrand,<sup>17</sup> in 1924, Loutfy,<sup>18</sup> in 1930, and Etcheverry,<sup>19</sup> in 1938, also stressed the hereditary aspects of exophthalmic goiter. The role played by infection in engendering latent and hereditary thyrotoxicosis was well illustrated by the report of Baylac,<sup>20</sup> in 1896; he described the case of a patient in whom the disease developed after postpartum peritonitis had set in; her 18 year old daughter exhibited exophthalmic goiter after typhoid fever. In 1898, Brower<sup>21</sup> and Holmes<sup>22</sup> each reported the cases of

8. Cantilena, P.: Sull'eredità del gozzo esoftalmico, *Sperimentale* 53:269, 1884.

9. Oesterreicher, F.: Zur Aetiologie des Morbus Basedowii, *Wien. med. Presse* 25:336, 1884.

10. Mackenzie, H. W. G.: Clinical Lectures on Graves' Disease, *Lancet* 2: 545 and 601, 1890.

11. Thyssen: Hérédité similaire dans un cas de maladie de Basedow, *Progrès méd.* 9:67, 1889.

12. West, S.: Two Cases of Exophthalmic Goiter in Sisters, with Morbus Cordis and a History of Rheumatic Fever in Both, *Lancet* 1:1248, 1895.

13. Sottas, J.: Note sur le goître exophthalmique familial, *France méd.* 43:533, 1896.

14. Barret, G.: La maladie de Basedow dans l'enfance, Thesis, Paris, no. 109, 1901.

15. Brunet, J. L.: Contribution à l'étude clinique du goître exophthalmique dans l'enfance, Thesis, Lille, no. 30, 1919.

16. Vallery-Radot, P.: Dysthyroïdes familiales et héréditaires, Thesis, Paris, no. 158, 1921.

17. Lengrand, P. A.: Sur un cas de goître exophthalmique chez un enfant d'origine héréditaire à terminaison fatale, Thesis, Lille, 1924.

18. Loutfy, A.: Contribution à l'étude de la maladie de Basedow chez l'enfant, Thesis, Geneva, 1930.

19. Etcheverry, F. J.: Contribution à l'étude du traitement chirurgical de la maladie de Basedow chez l'enfant, Thesis, Bordeaux, 1938.

20. Baylac, J.: De l'hérédité simalaide dans de goître exophthalmique, *Arch. méd. de Toulouse* 2:30, 1896.

21. Brower, D. R.: Four Cases of a Family Type of Exophthalmic Goitre, *Chicago M. Rec.* 14:335, 1898.

22. Holmes, B.: Exophthalmic Goiter in Four Children in the Same Family, *Philadelphia M. J.* 1:1117, 1898.

4 patients with exophthalmic goiter in one family. In 1919, Souques and Lermoyez<sup>23</sup> described 7 cases of exophthalmic goiter in three generations among the 16 members of one family; the tendency to the disease seemed to be transmitted by the male members of the family. Climenko<sup>24</sup> quoted Carder, who, in discussing Levi's<sup>25</sup> cases, stated that "the mendelian law of heredity may be applied to exophthalmic goiter disease." In the same report, Climenko mentioned 1 case in which there was a familial history of the disorder in four consecutive generations, transmission occurring on the female side of the family in each case. Heiman<sup>26</sup> quoted Déjérine,<sup>27</sup> who, in 1886, stated the belief that exophthalmic goiter occurred particularly in neuropathic families. In 1928, Cockayne<sup>28</sup> reported a family in which 4 members in two generations had exophthalmic goiter. The disorder behaved as an irregular mendelian dominant, and Cockayne expressed the opinion that a constitutional weakness of the thyroid gland was inherited rather than the disease itself. Cockayne stated that "the transmission frequently occurs through apparently normal individuals, with the disease affecting grandparent and grandchild, aunt and niece, etc." In 1928, McGraw<sup>29</sup> found familial goiter in 29 per cent of 64 cases of exophthalmic goiter. In the same year, Morrison<sup>30</sup> reported 6 cases of exophthalmic goiter in one family and 2 in each of two other families. In their survey of 91 cases made in 1932, Rankin and Priestley<sup>31</sup> found "a positive family history of goiter in 22 per cent, usually of the exophthalmic goiter type." In 1935, Petit-Dutaillis and Péron<sup>32</sup> described familial exophthalmic goiter in 3 sisters. Of 6 patients with

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23. Souques and Lermoyez, J.: Goitre exophtalmique héréditaire et familial, *Rev. neurol.* **26**:20, 1919.

24. Climenko, H.: Heredity in Exophthalmic Goiter, *Arch. Neurol. & Psychiat.* **3**:530 (May) 1920.

25. Levi, L.: La lésion thyroïdienne fondamentale de la maladie de Basedow, *Rev. neurol.* **21** (pt. 2):631, 1913.

26. Heiman, H.: Exophthalmic Goiter in Childhood with Some Unusual Manifestations, *Am. J. Dis. Child.* **26**:216 (Sept.) 1923.

27. Déjérine: Le goitre exophtalmique et ses modalités frustes, graves, et aiguës; pronostic; traitement, *Rev. internat. de méd. et de chir.* **24**:103, 1913.

28. Cockayne, E. A.: Influence of Heredity in Exophthalmic Goiter, *Arch. Dis. Childhood* **3**:227, 1928.

29. McGraw, A. B.: Juvenile Exophthalmic Goiter, *Surg., Gynec. & Obst.* **47**:25, 1928.

30. Morrison, H.: The Familial Incidence of Exophthalmic Goiter, *New England J. Med.* **199**:85, 1928.

31. Rankin, F. W., and Priestley, J. T.: Exophthalmic Goiter in Children with a Review of Ninety-One Cases, *West. J. Surg.* **40**:498, 1932.

32. Petit-Dutaillis, D., and Péron, N.: Maladie de Basedow familiale, *Progrès méd.*, 1935, p. 1011.

hyperthyroidism reported by Lehman<sup>33</sup> in 1936, 3 gave a familial history of the disease. In 1939, McKnight<sup>34</sup> stated that "heredity undoubtedly is a factor in a number of cases [of hyperthyroidism]." In 1941, Kerley<sup>35</sup> reported that in girls with exophthalmic goiter, mother-daughter complexes were not infrequently present; in 24 of 104 cases, thyroid disease was present in the mother or members of the immediate family. In the same year, Black and Webster<sup>36</sup> observed that in 6 of 18 cases of exophthalmic goiter there was a familial history of the disease. Steiner and Newcomb<sup>37</sup> showed that in 19 of 34 families with thyroid disease there were also cases of diabetes. In 13 of these 19 families, the members with juvenile diabetes had palpable thyroid glands also. Thyroidectomy was performed on 14 patients, namely, 4 mothers, 2 fathers, 2 uncles and 6 aunts. It also is of interest to note the following unusual case reports: White<sup>38</sup> and Ochsner and Thompson<sup>39</sup> each reported exophthalmic goiter in an infant born of a mother afflicted with the disease during pregnancy. Sweet<sup>40</sup> described a case in which goiter developed in a newborn infant whose mother had colloid enlargement of the thyroid gland. Twin sisters and twin brothers with hyperthyroidism were reported respectively by Neff<sup>41</sup> and Fife.<sup>42</sup>

#### SUMMARY OF THE LITERATURE ON THE FAMILIAL ASPECTS OF JUVENILE EXOPHTHALMIC GOITER

A detailed survey of the literature was made for all cases of exophthalmic goiter in children up to and including the age of 16 years. For the construction of the table, 1,586 cases in this category were reviewed. Since many authors failed to indicate the presence or the absence of a familial history of thyroid dyscrasia, only 93 or 5.8 per cent of the total number of cases studied were eligible for the table. This low

33. Lehman, J. A.: Hyperthyroidism in Children, *West. J. Surg.* **44**:528, 1936.

34. McKnight, R. B.: Goiter in Adolescents with Special Reference to Hyperthyroidism, *J. South Carolina M. A.* **35**:168, 1939.

35. Kerley, C. G.: Hyperthyroidism in Children, *Arch. Pediat.* **58**:92, 1941.

36. Black, J. B., Jr., and Webster, B.: Hyperthyroidism in the Adolescent, *J. Clin. Endocrinol.* **1**:859, 1941.

37. Steiner, M. M., and Newcomb, A. L.: Enlargement of the Thyroid Gland in Juvenile Patients with Diabetes Mellitus, *Am. J. Dis. Child.* **61**:458 (March) 1941.

38. White, C.: A Foetus with Congenital Hereditary Graves' Disease, *J. Obst. & Gynaec. Brit. Emp.* **21**:231, 1912.

39. Ochsner, A. J., and Thompson, R. L.: The Surgery and Pathology of the Thyroid and Parathyroid Glands, St. Louis, C. V. Mosby Company, 1910, p. 192.

40. Sweet, P. W.: Goiter in Newborn Infant, *Northwest Med.* **27**:183, 1928.

41. Neff, F. C.: Exophthalmic Goiter in Identical Twin Girls, *J. Pediat.* **1**:239, 1932.

42. Fife, J. K.: Diffuse Toxic Goiter Occurring in a Pair of Identical Twins, in Frank Howard Lahey Birthday Volume, Springfield, Ill., Charles C. Thomas, Publisher, 1940, p. 169.

percentage of familial exophthalmic goiter in juvenile patients, therefore, does not reflect the actual incidence of the familial factor in causing this disease. Our calculations of Atkinson's data<sup>43</sup> showed that 39, or 18.8 per cent, of a series of 208 patients with juvenile exophthalmic goiter whose cases were compiled by him gave a familial history of thyroid disease, but for the reason already stated, we are inclined to believe that these figures likewise fail to represent the true incidence of familial influences in causing juvenile exophthalmic goiter.

In this series of 93 patients with familial thyroid dyscrasia, 74, or 79 per cent, were female, and 19, or 21 per cent, were male (female: male = 3.9:1). The 93 patients were members of 66 families; 20 were sisters; 6 were mixed siblings, and 2 were brothers. In the cases of the 74 female patients with juvenile exophthalmic goiter, a positive history of thyroid disease was obtained for the mothers of 30 of these and for the fathers of 11. In the cases of the 19 male patients, the mothers of 9 and the fathers of 3 were afflicted with some form of thyroid dyscrasia. In both groups, therefore, the incidence of thyroid disease in mothers was three times as great as in fathers.

#### MEDICAL AND SURGICAL ASPECTS OF JUVENILE EXOPHTHALMIC GOITER

Clinically, the picture of juvenile exophthalmic goiter resembles the adult type. However, in its early stages it is often overlooked, especially when exophthalmos is not well developed, since the emotional instability, the restlessness and the fidgeting are not infrequently attributed to a childish lack of poise.

The immediate effects of subtotal thyroidectomy are as beneficial to juvenile exophthalmic goiter as to the adult type. It is the ultimate result that is often in doubt. One is always confronted with the question of what will happen when the child reaches the eighteenth year.

The preoperative handling of juvenile patients is similar to that of adults. The actual extent of operation, however, presents a controversial problem. Two schools of thought exist concerning the amount of gland to be removed. On the one hand, the belief is held that in young patients more gland should be retained than is usual in order to avoid too sudden an upset in the endocrine balance at a time in life when the hormonal interrelation is under particular stress. On the other hand, there are those who believe that the regenerative quality of the thyroid gland is more active in the young patient and that, consequently, too much gland cannot be removed.

43. Atkinson, F. R. B.: Exophthalmic Goiter in Children, *Brit. J. Child. Dis.* 35:165 and 267, 1938.

*Survey of the Literature on Familial Aspects of Juvenile Exophthalmic Goiter*

Author	Case	Age	Sex	Relation	Familial History
Hawkes, J.: <i>Lancet</i> 2: 131, 1861	1	5½ yr	F	.....	Father had exophthalmic goiter
Bouehut, E.: <i>Traité pratique des maladies des nouveau-nés</i> , ed. 5, Paris, J. B. Baillière & fils, 1867, p. 273	2	13 yr.	F	.....	Cousin had goiter
Solbrig: <i>Allg. Ztschr. f. Psychiat.</i> 27: 5, 1871	3	8 yr.	M	.....	Mother had exophthalmic goiter
Demme, R., in Gerhardt, C.: <i>Handbuch der Kinderkrankheiten</i> , Tübingen, H. Laupp, 1878, vol. 3, pt. 2, p. 397	4	3½ yr.	F	.....	Mother and father had goiter
Ehrlich, H.: <i>Ueber Morbus Basedowii im kindlichen Alter</i> , Thesis, Berlin, G. Schade, 1890	5	11 yr.	F	.....	Sister had exophthalmic goiter
Kronthal, P.: <i>Klin. Wehnsehr.</i> 36: 650, 1893	6	12 yr.	F	.....	Mother had exophthalmic goiter
Steiner, F.: <i>Arch. f. Kinderh.</i> 20: 321, 1896; 21: 128, 1896	7	9 yr.	F	.....	Grandmother had goiter
Holmes <sup>22</sup> .....	8 9 10 11	4½ yr. 7 yr. 9½ yr. 12 yr.	M F F F	} Brother and sisters	
Gillepsie, A. L.: <i>Brit. M. J.</i> 2: 1042, 1898	12 13 14	9 yr. 11 yr. 10 yr.	M F F		
Ovussa, V.: <i>Riforma med.</i> 2: 153, 1902	15 16 17	7 yr. 5 yr. 11 yr.	M F F	} Brother and sisters	
Trischitta, V.: <i>Pediatrics</i> 11: 74, 1903	18	13 yr.	M	.....	Father and 2 sisters had exophthalmic goiter
Lewinberg, G.: <i>Morbus Basedowii im Kindesalter</i> , Thesis, Leipzig, B. Georgi, 1904	19 20 21	11 yr. 14 yr. 13 yr.	F F F	} Sisters	
	22 23 24	12 yr. 11 yr. 10 yr.	M F F		
	25	11 yr.	F	.....	Mother had struma
Mathes, V.: <i>Ueber die heutigen Anschauungsweisen über Theorie und Therapie der Basedow'schen Krankheit mit kasuistischen Beiträgen</i> , Thesis, Halle, C. A. Kaemmerer & Co., 1905; cited by Sattler. <sup>1</sup>	26	10 yr.	M	.....	Mother had exophthalmic goiter
Dubreuil-Chambardel, L.: <i>Provençe méd.</i> , May 25, 1907; cited by Vallery-Radot. <sup>10</sup>	27 28	4 yr. 7 yr.	F F	} Sisters	Mother and maternal grandmother had exophthalmic goiter
Taubmann, H.: <i>Ueber Morbus Basedowii im Kindesalter</i> , Basel, J. Kohlhepp, 1907	29 30	11 yr. 10 yr.	F F		
Frey, E.: <i>Jahresb. ü. d. Leistung. d. Neurol. u. Psychiat.</i> 13: 753, 1909	31	15 yr.	F	.....	Father, 1 sister and 1 brother had exophthalmic goiter
Nieoll, M.: <i>M. Rec.</i> 75: 667, 1909	32	10 yr.	F	.....	Brother and father had exophthalmic goiter
Ochsner and Thompson <sup>30</sup> .....	33	5 weeks	M	.....	Exophthalmic goiter developed in mother during pregnancy
White <sup>38</sup> .....	34	At birth	M	.....	Exophthalmic goiter developed in mother during fifth month of pregnancy
Raillet, G.: <i>Bull. et mém. Soc. méd. d. hôp. de Paris</i> 37: 708, 1914	35	7½ yr.	F	.....	Father and grandmother had exophthalmic goiter
Moss, M. I.: <i>New York M. J.</i> 99: 482, 1914	36 37	11 yr. 4 yr.	M F	} Brother and sister	Mother had exophthalmic goiter
Sawyer, A. W.: <i>Ann. Surg.</i> 64: 371, 1916	38	10 yr.	F	.....	Aunt had toxic goiter

*Survey of the Literature on Familial Aspects of Juvenile Exophthalmic Goiter—Continued*

Author	Case	Age	Sex	Relation	Familial History
Harvler, P.: <i>Paris méd.</i> 9: 457, 1919	39	12 yr.	M	.....	Mother, grandmother, maternal aunt and paternal aunt had exophthalmic goiter
Chimenko <sup>24</sup> .....	40 41	10 yr. 6 yr.	M } F }	Brother and sister	Mother and maternal aunt had exophthalmic goiter; maternal grandmother had enlarged thyroid; maternal aunt had goiter; great grandmother, her 3 daughters and 1 niece had exophthalmic goiter
Frantz, M. H.: <i>New York M. J.</i> 113: 275, 1921	42	9 yr.	F	.....	Mother had hyperthyroidism
Cole, W.: <i>Arch. Pediat.</i> 40: 703, 1923	43	12 yr.	F	.....	Mother had goiter
Nouviale, L.: <i>Contribution à l'étude de la maladie de Basedow dans l'enfance</i> , Thesis, Paris, no. 90, 1923	44 45	13½ yr. 4 yr.	F } F }	Sisters	
Wheelon, H.: <i>Endocrinology</i> 7: 437, 1923	46	4½ yr.	F	.....	Mother and father had prominent eyes
Longrand <sup>25</sup> .....	47	10 yr.	F	.....	Paternal grandmother had exophthalmic goiter
Wilner, A. S.: <i>M. J. &amp; Rec. (suppl.)</i> 120: 185, 1921	48 49 50 51	10 yr. 13 yr. 8 yr. ?	F } F } F } F }	Sisters Sisters	
	52 53	12 yr. ?	F } F }	Sisters	
Burnet, J.: <i>Internat. Clin.</i> 1: 91, 1925	54	9 yr.	F	.....	Mother had exophthalmic goiter
Helmholz, H. F.: <i>J. A. M. A.</i> 87: 157 (July 17) 1926	55	3 yr.	M	.....	Aunt and maternal grandmother had exophthalmic goiter
	56 57	11 yr. ?	F } F }	Sisters	
Fried, C.: <i>Zentralbl. f. Chir.</i> 55: 2196, 1928	58	11 yr.	F	.....	Mother had exophthalmic goiter
McGraw <sup>26</sup> .....	59 60	6 yr. 7 yr.	F } F }	Sisters	Paternal grandfather had exophthalmic goiter
Morrison <sup>26</sup> .....	61 62	? ?	F } F }	Sisters	
	63 64	? ?	F } F }	Sisters	
Sweet <sup>26</sup> .....	65	Newborn infant	..	.....	Mother had colloid enlargement of the thyroid
Dinsmore, R.: <i>Proc. Internat. Assemb. Interstate Post-Grad. M. A. North America</i> , 1929, p. 484	66	13½ yr.	M	.....	Brother had exophthalmic goiter
Braid, F., and Neale, A. V.: <i>Arch. Dis. Childhood</i> 5: 229, 1930	67 68	2½ yr. 16 yr.	M } M }	Brothers	
Loutfy <sup>28</sup> .....	69	14½ yr.	F	.....	Father had exophthalmic goiter
Miller, H. C.: <i>Nebraska M. J.</i> 15: 363, 1930	70	8½ yr.	F	.....	Maternal grandmother had exophthalmic goiter
Kerley, O. G.: <i>Arch. Pediat.</i> 48: 61, 1931	71	3½ yr.	F	.....	Mother had pronounced goiter
Shouse, S. S.: <i>Am. J. Surg.</i> 11: 124, 1931	72	5 yr.	F	.....	Two maternal aunts had nontoxic goiter; mother had mild hyperplasia of the thyroid gland; cousin died 5 months after operation for goiter
Abbott, A. C.: <i>Internat. Clin.</i> 4: 98, 1932	73	14 yr.	F	.....	Mother had exophthalmic goiter



*Survey of the Literature on Familial Aspects of Juvenile Exophthalmic Goiter—Continued*

Author	Case	Age	Sex	Relation	Familial History
Neff <sup>41</sup> .....	74 75	9½ yr. 9½ yr.	F } F }	Twins	Aunt had goiter
Jones, C. K.: J. A. M. A. 103: 914 (Sept. 22) 1934	76	10 yr.	M	.....	Father had hyperthyroidism
Elliot, P. O.: J. Pediat. 6: 205, 1935	77 78	2½ yr. ?	F } F }	Sisters	Mother had goiter during youth
Heuyer, Nicholas and Stern: Bull. Soc. de pédiat. de Paris 33: 293, 1935	79	11 yr.	M	.....	Mother and aunt had exophthalmic goiter
Rose, E.; Rose, E. K., and Pendergrass, E. P.: J. Pediat. 7: 325, 1935	80	14 yr.	F	.....	Mother had goiter during youth
Lehman <sup>23</sup> .....	81	4 yr.	F	.....	Two maternal aunts and 1 grand aunt had exophthalmic goiter
	82 83	? ?	F } F }	Sisters	Mother had nontoxic goiter
	84 85	? ?	F } F }	Sisters	Mother had nontoxic goiter
Bellby, G. E., and McClintock, J. C.: New York State J. Med. 37: 563, 1937	86	4 yr.	F	.....	Grandmother had exophthalmic goiter
Nixon, N.: J. Pediat. 18: 71, 1941	87	8 yr.	F	.....	Paternal grandmother had goiter
	88	6½ yr.	F	.....	Maternal uncle had goiter
	89	12½ yr.	F	.....	Mother had exophthalmic goiter
Steiner and Newcomb <sup>27</sup> .....	90	7 yr.	F	.....	Mother had goiter
	91	8 yr.	F	.....	Mother had exophthalmic goiter
Moolten, R. R., and Bruger, M.: Present article	92	11 yr.	F	.....	Mother operated on for exophthalmic goiter
	93	15 yr.	F	.....	Father operated on for exophthalmic goiter

Our personal practice is to leave little gland, pursuing the same technic as when operating on adult patients. We strongly agree with the dictum that operation will always cure exophthalmic goiter but only when the operation is adequately performed.

#### REPORT OF CASES

CASE 92.—T. S., a girl aged 11 years, was first seen on April 1, 1940. On Jan. 12, 1940, one of us (R. R. M.) had operated on the mother of the patient for exophthalmic goiter when she was 45 years of age. As far as could be ascertained, no other member of the family, immediate or remote, had suffered from this disease.

Her mother stated that for the past few months, the child had been extremely excitable, nervous and fidgety and was continuously making purposeless movements. However, her work at school was good. She had recently shown rapid growth in height. Otherwise, the past history was irrelevant.

Physical examination revealed a tall and thin child presenting no evidence of maturity. The eyes were markedly exophthalmic. The thyroid gland was symmetrically enlarged and soft, although some nodules could be palpated on deep pressure. There was a pronounced tremor of the fingers, and the pulse rate was 140. The basal metabolic rate was 31 per cent above the average normal.

The mother refused operation at this time. The patient was seen again on April 15 and on May 18. The exophthalmos and the swelling of the neck were now more pronounced and the tachycardia more marked. Emotional instability also had increased. On May 21, the patient was hospitalized. The basal metabolic rate on admission was 32 per cent above the average normal. After nine days of preoperative preparation with compound solution of iodine, U. S. P. (Lugol's solution), the basal metabolic rate fell to 10 per cent above the average normal. On June 1, with the patient under anesthesia induced with cyclopropane and oxygen, bilateral thyroidectomy was performed; this was complete on the right side except for a thin layer left over the posterior capsule, and six sevenths of the left lobe was excised.

Histologic examination of the thyroid tissue as reported by the pathologist revealed "thyroid hyperplasia of the exophthalmic goiter type."

*Clinical Course.*—The patient was discharged from the hospital on the sixth postoperative day after an uneventful course. The last follow-up report was made on Feb. 21, 1941. The patient felt well and gained in weight, and the pulse rate was 78 per minute.

CASE 93.—R. B., a girl aged 15, was first seen in the thyroid clinic on Nov. 1, 1938. On Feb. 14, 1935, one of us (R. R. M.) had operated on the father of this patient for exophthalmic goiter when he was 50 years old. As in the previous case, no other member of the family was known to have suffered from this disease.

The patient complained of nervousness and increased appetite for six months and of cardiac palpitation for seven months. The past history was essentially negative. She began to menstruate at the age of 12 and followed a regular cycle from then on without dysmenorrhea.

On physical examination, the lack of poise and the inability to keep still for any length of time were outstanding features. All the classic eye signs were present, namely, the Stellwag, Dalrymple, Möbius and von Graefe signs. The thyroid gland was symmetrically enlarged; thrill and bruit over the gland were present. There were marked tachycardia and pronounced tremor of the fingers. The tonsils were enlarged and hyperemic. The basal metabolic rate on November 4 was 39 per cent above the average normal.

The patient was hospitalized on Feb. 18, 1939. Nine days later, after adequate preparation with compound solution of iodine, U. S. P., and with the patient under anesthesia induced with ethylene, extensive thyroidectomy was performed, removing roughly fourteen fifteenths of each lobe.

The histologic examination of the thyroid tissue as reported by the pathologist indicated "exophthalmic goiter in a stage of relative remission."

*Clinical Course.*—On the seventh postoperative day (March 6), the basal metabolic rate was 6 per cent below the average normal. The patient was discharged from the hospital on March 8 after an uneventful postoperative course.

The follow-up history was rather interesting. The patient did well for about a month; after this, tachycardia developed, the rate ranging between 112 and 140 per minute. On June 28, tonsillectomy was performed. However, in spite of progressive gain in weight and normal basal metabolic determination, tachycardia persisted. The question of either persistent or recurrent hyperthyroidism arose, but in view of the repeated normal metabolic studies and the absence of any palpatory evidence of regrowth of the thyroid gland, this was ruled out. On August

24, an electrocardiogram showed sinus tachycardia. In October 1939, three high voltage roentgen treatments were given over the thyroid region, but this failed to influence the tachycardia.

At the time of writing, this patient is still being followed in the thyroid clinic; tachycardia persists, although subjectively she feels well.

#### SUMMARY

The extensive literature on juvenile exophthalmic goiter is reviewed, and special emphasis is given to the familial aspects of this disease. Ninety-one cases of familial exophthalmic goiter in children are surveyed, and the possible familial source of the thyroid dyscrasia is indicated. In addition, 2 new cases occurring in children aged 11 and 15 years, respectively, are presented; in the first of these, the mother had subtotal thyroidectomy for exophthalmic goiter, and in the second, partial thyroidectomy was done on the father for the same disorder.

Julius Wiland, B.S., assisted in surveying the literature and in preparing the bibliography.

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# PHYSIOLOGIC CHANGES ASSOCIATED WITH VARICOSE VEINS AND THEIR CORRECTION

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With increasing experience in the care of patients with varicose veins, the importance of fundamental physiologic changes in the production of the patient's symptoms and the importance of their correction in the treatment of the patient have been progressively emphasized. And in an experience with now well over 2,000 patients with varicose veins, I have become convinced that only the type of treatment which corrects or compensates for derangements in normal function is of more than temporary success.

The veins of the leg have two functions, viz., to return blood to the heart and to serve as a reservoir for the storage of blood for use in emergencies.<sup>1</sup> In the latter function they are responsive to the same influences which affect the other longer and better known organs with similar function. Of the 1,000 cc., more or less, of depot blood in the spleen, the liver, the lung bed, the mesenteric veins and the legs, 300 to 400 cc. is normally found in the legs, and most of this is in the superficial venous system.<sup>1</sup> The exact amount changes in response to local or central stimuli through direct<sup>2</sup> or reflex action of the sympathetic nervous system. But the reactions of the veins and consequently the depot function are lost with the development of varicosities<sup>1</sup> and varicose veins, which, even though they may contain more blood than normal vessels, are unable to mobilize it in time of need. This loss of depot function may be of some importance in the production of some of the milder symptoms associated with varicose veins. It probably accounts, in part at least, for the lassitude and easy fatigability of which some of these patients complain.

The return of venous blood from the capillaries to the heart is the more important function of the veins and is accomplished by two, and possibly three, separate and distinct mechanisms (fig. 1). The first of these is capillary blood pressure; the second, the action of the intrinsic

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1. Franklin, K. J.: Monograph on Veins, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

2. Franklin, K. J., and McLacklin, A. D.: Dilatation of Veins in Response to Tapping in Man and in Certain Other Mammals, *J. Physiol.* 88:257-260, 1936.

muscles of the leg in conjunction with competent venous valves, and the third, the movement of the diaphragm and changes in intrathoracic pressure associated with respiration.<sup>3</sup> Respiratory movements create a negative pressure in the thorax, and this in addition to the pumping action of the diaphragm undoubtedly aids in venous return. That respiratory motion alone is entirely insufficient to overcome the force of gravity in man in the upright position is conclusively shown by the con-

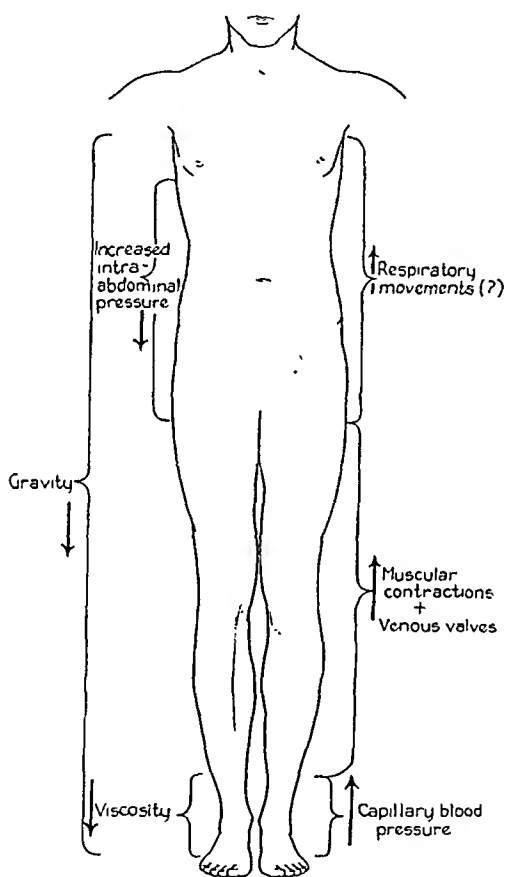


Fig. 1.—Factors retarding venous return are shown on the left; those favoring venous return are shown on the right.

stant finding of a venous pressure of approximately 35 cm. of water in the normal femoral vein in the groin.<sup>4</sup>

3. Runge, H.: Ueber der Verandrucke in Schwangerschaft, Geburt und Wochenbett, *Arch. f. Gynäk.* **122**:142-151, 1924.

4. McPheeters, H. O.; Merkert, C. E., and Lundblad, R. A.: Mechanics of Reverse Flow of Blood in Varicose Veins as Proved by Blood Pressure Readings, *Surg., Gynec. & Obst.* **55**:298-302, 1932.

Normal capillary blood pressure at the venous end amounts to only 10 or 12 mm. of mercury,<sup>5</sup> a force entirely insufficient to overcome gravity and return blood to the heart in the upright position under normal conditions. Under abnormal conditions it may be called on to contribute greatly to venous return, but in this event unpleasant side effects are to be expected; these will be discussed later. The interplay between normal venous valves and the unceasing contraction, tonic and otherwise, of the intrinsic muscles of the leg are responsible for venous return.

In the normal vein with competent valves the application of external pressure causes displacement of the contents in the direction permitted by the valves, i. e. toward the heart. When this pressure is released, a competent valve prevents regurgitation of blood from above, and the segment can fill from below only (fig. 2). As the blood is drawn toward the heart, the venous pressure distal to this point is lowered.<sup>6</sup> Constant

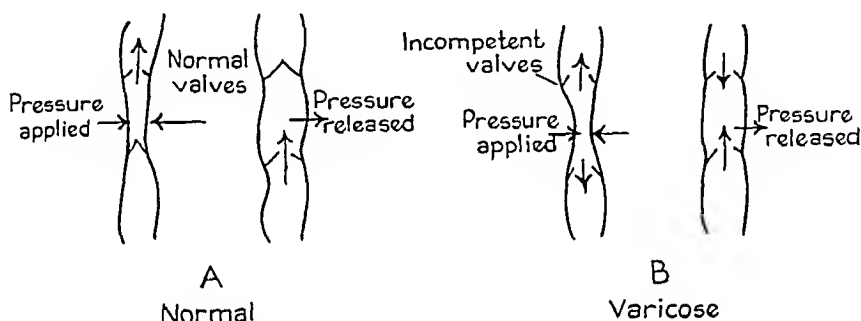


Fig. 2.—The effect of external pressure on (A) normal veins and (B) varicose veins.

repetition of this process is the great factor in venous return from the legs in normal persons. Even a single slight contraction of the muscles of the leg can cause a fall of 40 cm. of water in venous pressure when this is measured directly in the veins of the leg.<sup>1</sup>

With the development of varicose veins the valves become incompetent either from inflammatory destruction of valve leaflets<sup>7</sup> or from

5. Landis, E. M.: (a) Capillary Pressure and Capillary Permeability, *Physiol. Rev.* **14**:404-481, 1934; (b) Capillary Pressure and Hyperemia in Muscle and Skin of the Frog, *Am. J. Physiol.* **98**:704-716, 1931; (c) Capillary Pressure in Frog Mesentery, *ibid.* **75**:548-579, 1926.

6. Anrep, G. V., and Von Saalfeld, E. V.: The Blood Flow Through the Skeletal Muscle in Relation to Its Contraction, *J. Physiol.* **85**:375-399, 1935. Hooker, D. R.: Evidence of Functional Activity on the Part of Capillaries and Veins, *Physiol. Rev.* **1**:112, 1921; The Effect of Exercise on the Venous Blood Pressure, *Am. J. Physiol.* **28**:235-248, 1911.

7. Edwards, E. A., and Edwards, J. E.: Effect of Thrombophlebitis on Venous Valves, *Surg., Gynec. & Obst.* **65**:310-320, 1937.

dilatation of the wall of the vein, which when it reaches one and one-half to twice the normal size, does not allow coaptation of valve cusps and these are thus rendered useless.<sup>8</sup> This incompetence of venous valves in varicose veins vitiates the effect of the peripheral venous heart, since the application of external pressure to a segment of vein in which the valves are incompetent displaces blood both toward and away from the heart. When pressure is released, the segment fills both from above and from below, and there is no effect on venous return or on venous pressure distal to this point (fig. 2).

By direct measurement Beecher<sup>9</sup> found that the pressure in the normal long saphenous vein at the level of the ankle during walking fluctuated from a minimum of 30 cm. of water (a pressure less than normal capillary blood pressure) to a maximum of 50 to 75 cm. of water. Under identical conditions the pressure in the varicose long saphenous vein remains at a level constantly above normal capillary blood pressure (95 cm. of water).

Furthermore, when venous valves are incompetent, as they are in varicose veins, blood is free to flow in any direction in response to differences in hydrostatic pressure. When the patient with superficial varicose veins of the leg walks, the peripheral venous heart of the deep veins works well, and venous pressure is lowered in the deep veins. In the superficial veins, however, the peripheral venous heart is not effective, and venous pressure remains high. Blood tends to flow from superficial incompetent veins to deep veins in response to differences in hydrostatic pressure. When the varices extend to the saphenofemoral junction, the pressure in the upper end of the saphenous vein is less owing to gravity than that in the femoral vein, and blood tends to flow from the normal femoral vein to the varicose saphenous vein in the thigh. It then reenters the deep veins in the leg at a point distal to its origin (fig. 3). This retrograde flow of blood in superficial varices may be demonstrated clinically by the Trendelenburg test<sup>10</sup> or by fluoroscopic observation of the course taken by radiopaque material injected into a varix.<sup>11</sup> When observed in this manner the mixture of

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8. Edwards, E. A.: Orientation of Venous Valves in Relation to Body Surfaces, *Anat. Rec.* **64**:369-385, 1936.

9. Beecher, H. K.: Adjustment of the Flow of Tissue Fluid in the Presence of Localized, Sustained High Venous Pressure as Found with Varices of the Great Saphenous System During Walking, *J. Clin. Investigation* **16**:733-739, 1937.

10. Trendelenburg, F.: Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvaricen, *Beitr. z. klin. Chir.* **7**:195-210, 1891.

11. (a) Allen, E. V., and Barker, N. W.: Roentgenologic Visualization of Veins of Extremities (Thorium Dioxide), *Proc. Staff Meet., Mayo Clin.* **9**:71-74, 1934. (b) Barker, N. W., and Camp, J. D.: Direct Venography in Obstructing Lesions and Veins, *Am. J. Roentgenol.* **35**:485-489, 1936. (c) de Takáts, G.;

radiopaque material and blood wells up through superficial varices as water from a spring or remains stationary so long as the patient stands still. As soon as the patient begins to exercise, the mixture flows distally and disappears rapidly into the deep veins of the lower leg.<sup>12</sup>

That the symptoms of patients with extensive superficial varices are not more severe may be due to the fact that since the deep veins normally return from 80 to 90 per cent of the blood from the leg, the addition of the 10 to 20 per cent ordinarily cared for by the superficial veins is of no physiologic importance. Even when the burden of the deep veins is increased by 50 per cent owing to the retrograde flow of blood, the

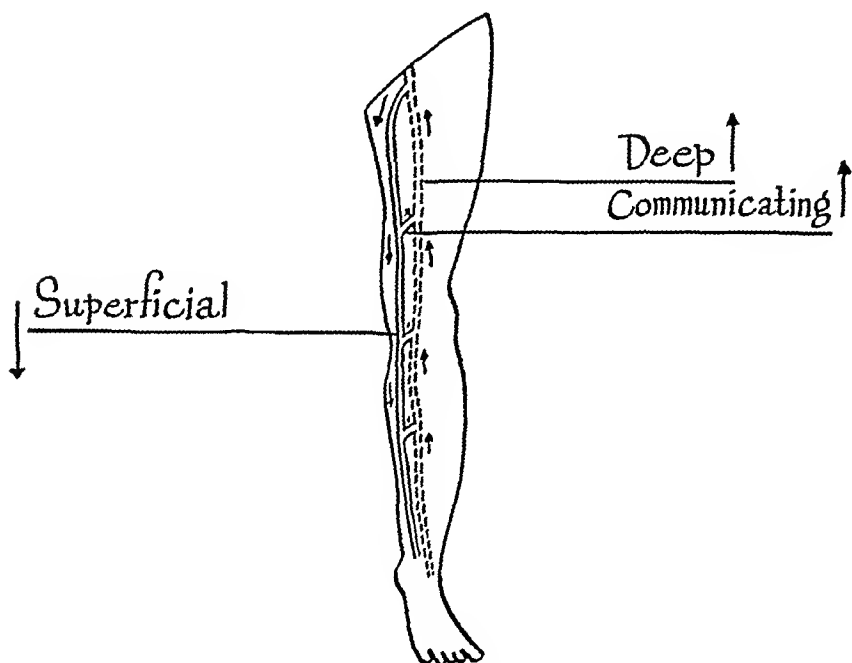


Fig. 3.—Direction of blood flow in patients with normal deep and communicating veins but with varicose superficial veins.

Quint, H.; Tillotson, B. I., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, *Arch. Surg.* **18**:671-686 (Feb.) 1929. (d) Faxon, H. H., and Barrow, D. W.: End Results in High Ligation and Injection of the Long Saphenous Vein, *Surgery* **3**:518-527, 1938. (e) Howard, N. J.; Jackson, C. R., and Mahon, E. J.: Recurrence of Varicose Veins Following Injection: A Study of the Pathologic Nature of the Recurrence and a Critical Survey of the Injection Method, *Arch. Surg.* **22**:353-376 (March) 1931. (f) Harrop, G. A., Jr., and Waterfield, R. L.: Effect of Posture on the Composition and Volume of Blood and on Its Selective Diffusion into the Lymph Spaces, *J. Physiol.* **70**:xxxii, 1930. (g) McPheeters, Merkert and Lundblad.<sup>4</sup>

12. McPheeters, Merkert and Lundblad.<sup>4</sup> de Takáts, Quint, Tillotson and Crittenden.<sup>11c</sup>



capacity of the deep veins is not taxed. And it is fair to say that when the deep veins are patent, the obliteration of superficial varicose trunks never hinders total venous return but rather aids this by lightening the burden of the deep veins.

This increased venous pressure found in varicose trunks is an important consideration in planning the treatment of patients with varicose veins, for unless corrected, it will provoke the recurrence of varices previously obliterated or the formation of new ones. Practically, this means operative interruption of the incompetent venous trunk and its branches at its junction with the deep veins. When this is not done, recurrence is the rule. Every single one of 100 consecutive patients with varicose veins reviewed by me who were treated by injection alone and in whom ligation was not done had recurrence. I have come to feel as do others<sup>13</sup> that the treatment of patients with superficial varicose veins by injection alone should be limited to those rare patients who give a negative reaction to the Trendelenburg test and who seek relief for cosmetic reasons alone.

On the other hand, in patients with varicose veins in whom the long and/or short saphenous veins are incompetent, the results of the combination of properly executed ligation and treatment by injection have been satisfactory.<sup>11d</sup> When there is also incompetence of a vein communicating between the deep and the superficial venous system in the thigh as determined by the multiple tourniquet test,<sup>14</sup> ligation is again indicated and should be done proximal to the junction with the superficial vein.<sup>15</sup> When this is not feasible technically, ligation of the lower part of the long saphenous vein is a less exact method of trying to accomplish the same thing. Postoperative sclerosis of all superficial varices is necessary for the most satisfactory cosmetic results. This procedure also has minimized the tendency to recurrence.<sup>11d</sup>

Increased pressure has another and more important effect on the circulation in that it provokes an increase in capillary blood pressure unless an alternate route of venous return through veins in which the pressure is normal can be found. When the deep and communicating veins of the lower leg are competent, such an alternate route exists, and

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13. Nicholson, B. B.: Varicose Veins: Etiology and Treatment; Clinical and Histologic Study, *Arch. Surg.* **15**:351-376 (Sept.) 1927; Histology, Pathology, and Etiology of Varicose Veins, *ibid.* **7**:47-63 (July) 1923. Faxon, H. H.: End Results in the Injection Treatment of Varicose Veins, *New England J. Med.* **208**: 357-361, 1933. Howard, Jackson and Mahon.<sup>11e</sup>

14. Barrow, W.: The Treatment of Varicose Veins, *J. Kentucky M. A.* **38**: 140-145, 1940.

15. Mahorner, H. R., and Ochsner, A.: A New Test for Evaluating Circulation in the Venous System of the Lower Extremity Effected by Varicosities, *Arch. Surg.* **33**:479-492 (Sept.) 1936. Faxon and Barrow.<sup>11d</sup>

disabling symptoms are uncommon. However, when either deep or communicating veins are incompetent, the venous pressure is raised throughout the tributary area (fig. 4), and the physiologic effects are identical with those produced experimentally by the application of an inflated sphygmomanometer cuff, the results of which have been studied by Landis.<sup>16</sup> Landis observed that the venous pressure promptly rose to levels above the pressure in the cuff (up to systolic blood pressure).<sup>17</sup> This increase in venous pressure was followed after an interval of fifteen to forty-five seconds by increase in the capillary blood pressure to levels

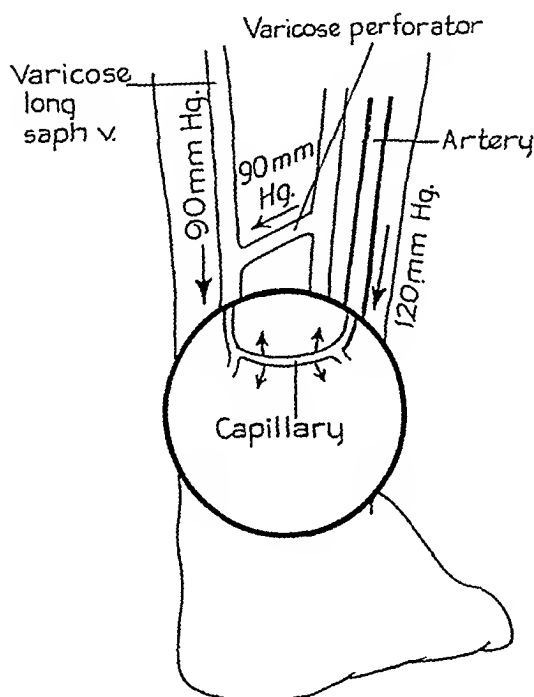


Fig. 4.—The effect of incompetence of both a perforator and a superficial vein on the capillary blood pressure and the exchange of fluid between the blood stream and the tissue space.

16. (a) Landis, E. M.: Capillary Blood Pressure in Mammalian Mesentery as Determined by the Micro-Injection Technique, *Am. J. Physiol.* **93**:353-362, 1934; (b) Micro-Injection Studies of Capillary Permeability: II. The Relation Between Capillary Pressure and the Rate at Which Fluid Passes Through the Walls of Single Capillaries, *ibid.* **82**:217-238, 1927; (c) III. Effect of Oxygen Lack, *ibid.* **83**:528-542, 1928; (d) Vascular Physiology and Clinical Medicine, *Ann. Int. Med.* **10**:290-298, 1936. (e) Landis, E. M.; Jones, L.; Angevine, M., and Erb, W.: The Passage of Fluid and Protein Through Human Capillary Wall During Venous Congestion, *J. Clin. Investigation* **11**:717-734, 1932.

17. Duffield, F. A., and Harris, I.: Increase of Pressure in Veins to the Level of Arterial Pressure Caused by Constricting the Limb in Which the Venous Pressure Is Recorded, *J. Physiol.* **81**:283-285, 1934.

of 8 to 10 mm. of mercury higher than the pressure in the cuff. Capillary hypertension in turn results in marked interference with capillary function, and when secondary to varicose veins, I believe is largely responsible for the severe symptoms and disabling complication sometimes encountered.

Capillary function is dependent on the properties of capillary endothelium as a semipermeable membrane allowing the free passage of fluid and simple molecules but restraining the complex protein molecules.<sup>18</sup>

In 1892 Starling<sup>19</sup> suggested that fluid moves from capillary to tissue space in response to physical forces. Subsequent investigation has confirmed this, for under normal conditions the hydrostatic blood pressure at the arteriolar end (45 cm. of water) is above the colloid osmotic pressure (36 cm. of water), and fluid tends to go from capillary to tissue space at the arteriolar end. The capillary hydrostatic pressure at the venous end (22 cm. of water) is less than the colloid osmotic pressure (36 cm. of water), and fluid tends to be drawn from tissue space into capillary space (fig. 5). This maintenance of normal fluid balance between capillary and tissue spaces is dependent on the maintenance of these relations.<sup>20</sup>

Unfortunately, in patients with extensive varices of the communicating or deep veins, as I have noted before, there is an elevation of the venous pressure which is reflected in increased capillary pressure. When the capillary pressure is elevated beyond normal limits, filtration of fluid into the tissues occurs at a rate proportional to the increase in the capillary pressure (fig. 6).<sup>21</sup> The rate of filtration increases with rise in temperature, being doubled by an increase of 14

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18. (a) Krogh, A.: *Anatomy and Physiology of Capillaries*, ed. 2, New Haven, Conn., Yale University Press, 1930. (b) Krogh, A.; Landis, E. M., and Turner, A. H.: *The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood*, *J. Clin. Investigation* **11**:63-95, 1932. (c) Landis, E. M.: *Micro-Injection Studies of Capillary Blood Pressure in the Human Skin*, *Heart* **15**:209-228, 1930; (d) *Passage of Fluid Through the Capillary Wall*, *Am. J. M. Sc.* **193**:297-313, 1937. (e) Rous, P.; Gilding, H. P., and Smith, F.: *The Gradient of Vascular Permeability*, *J. Exper. Med.* **51**:807-830, 1930. (f) Smith, F., and Rous, P.: *The Gradient of Vascular Permeability: IV. The Permeability of the Cutaneous Veins and Its Functional Significance*, *ibid.* **54**:499-514, 1931. (g) Landis, Jones, Angevine and Erb.<sup>16e</sup>

19. Starling, E. H.: *On the Absorption of Fluids from the Connective Tissue Spaces*, *J. Physiol.* **19**:312-326, 1895-1896.

20. Landis.<sup>16a</sup> Landis, Jones, Angevine and Erb.<sup>16e</sup>

21. Landis, E. M.: *Micro-Injection Studies of Capillary Permeability: I. Factors in the Production of Capillary Stasis*, *Am. J. Physiol.* **81**:124-142, 1927; footnotes 16a, 18c and 18d.

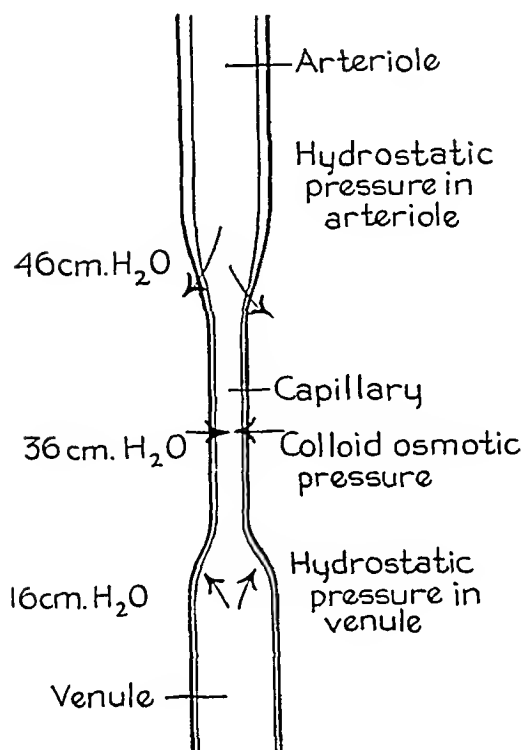


Fig. 5.—The normal exchange of fluid between the capillary and the tissue space.

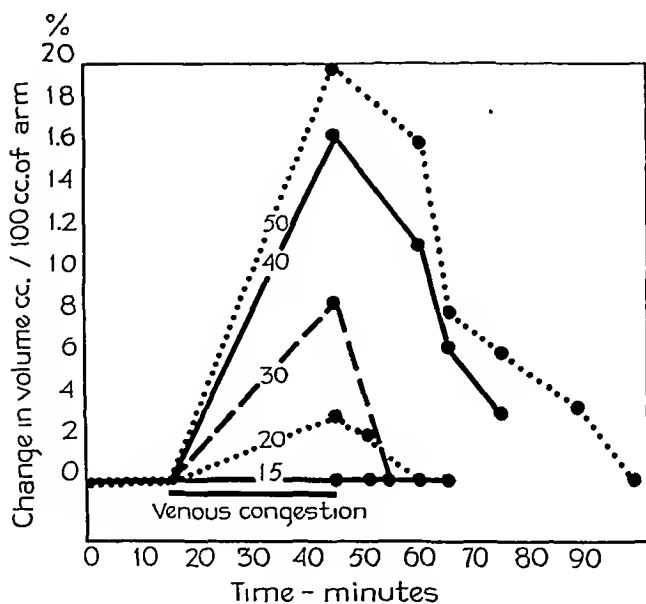


Fig. 6.—The effect of increased venous pressure on the accumulation of interstitial fluid (after Landis).

to 45 degrees (C.),<sup>22</sup> and patients with edema from any cause (varicose veins included) not infrequently have an exacerbation of symptoms during hot weather.

This increase in capillary pressure has another effect; normally the capillary loses an insignificant amount of protein (it is 96 per cent efficient according to Landis),<sup>23</sup> and this small amount is promptly removed by the lymphatics.<sup>24</sup> But when capillary pressure is raised to between 60 and 80 mm. of mercury, protein as well as fluid is lost in significant amounts (fig. 7),<sup>25</sup> thus decreasing the effective colloid osmotic pressure and favoring even greater filtration into the tissue spaces. This protein-rich fluid is also an ideal medium for fibroblastic proliferation, and if long present in the tissue spaces will per se provoke diffuse fibrosis of subcutaneous tissues<sup>26</sup> and may be as responsible as

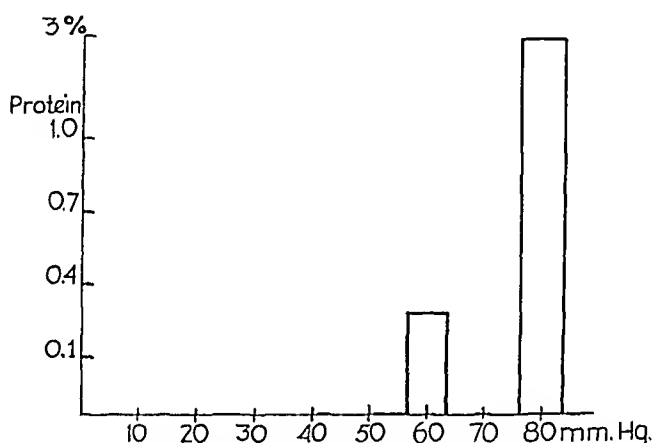


Fig. 7.—The amount of protein in lymph associated with different capillary pressures (after Landis).

22. (a) Landis, E. M., and Gibbon, J. H.: The Effect of Temperature and Tissue Pressure on the Movement of Fluid Through the Human Capillary Wall, *J. Clin. Investigation* **12**:105-138, 1933. (b) Landis.<sup>18c</sup>

23. Landis, E. M.: Factors Controlling Movement of Fluid Through the Human Capillary Wall, *Yale J. Biol. & Med.* **5**:201-225, 1933.

24. (a) Drinker, C. K.; Field, M. E., and Homans, J.: Experimental Production of Edema and Elephantiasis as Result of Lymphatic Obstruction, *Am. J. Physiol.* **108**:509-520, 1934. (b) Drinker, C. K., and Field, M. E.: *Lymphatics, Lymph, and Tissue Fluid*, Baltimore, Williams & Wilkins Company, 1933.

25. (a) Peters, J. P.: *Body Water: Exchange of Fluids in Man*, Springfield, Ill., Charles C. Thomas, Publisher, 1934. (b) Wright, S.: *Applied Physiology*, ed. 3, London, Oxford University Press, 1929. (c) Landis.<sup>5a</sup> (d) Landis.<sup>23</sup>

26. Zimmermann, L. M., and de Takáts, G.: The Mechanism of Thrombophlebitic Edema, *Arch. Surg.* **23**:937-953 (Dec.) 1931. Drinker, Field and Homans.<sup>24a</sup>

bacterial infection for the scarring and fibrosis sometimes associated with varicose ulceration.

The rate of filtration of fluid through capillary endothelium is dependent also on the amount of fluid already in the tissue spaces, decreasing as the amount of fluid in the tissue spaces increases. Landis observed that edema formed just one fourth as rapidly at the end of an hour as it had when capillary pressure was first elevated. He attributed this to the elastic resistance with which tissues oppose distention and named this phenomenon tissue tension. He found experimentally that tissue tension reached a maximum force of 35 mm. of mercury, and this long before the 10 per cent increase in volume which is necessary for the clinical detection of edema occurred.<sup>27</sup> That this force is a temporary one is shown by the fact that edema does develop eventually, but even then tissue elasticity continues to have some effect, for skin excised from an edematous extremity will shorten more than that taken from a normal one.<sup>22a</sup>

This tissue tension or elasticity is regained but slowly once sufficient fluid has accumulated to produce clinical edema. This slowness can be compensated for therapeutically, however, by the application of external elastic compression. This may explain in physiologic terms, i. e. the substitution of or addition of external compression to internal tissue tension, the almost universal success obtained with the use of elastic bandage, Unna's boot, elastic adhesive plaster and similar devices in the treatment of varicose ulceration. And since tissue tone is regained but slowly by patients with edematous extremities, I advise patients to continue to wear some sort of external elastic support for some time after the removal of the underlying cause—in this instance, varicose veins. I believe this support hastens recovery and minimizes subcutaneous fibrosis. For the same reason, I sometimes advise Buerger-Allen exercises.

This separation of the tissues with abnormal collections of fluid interferes mechanically with the exchange between tissues and capillary, as was shown by Harrison and Pilcher.<sup>28</sup> These investigators measured the oxygen tension in the venous blood returning from an edematous extremity and noted that it was greater than that in venous blood from a normal limb. For carbon dioxide the relation was reversed, i. e. the edematous extremity was functionally inefficient owing, I believe, to mechanical interference with the exchange of gases between tissue cell and capillary blood stream by abnormal collections of interstitial fluid.

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27. Footnotes 5 a, 18 b, 18 d, 22 a and 23.

28. Harrison, T. R., and Pilcher, C.: Studies in Congestive Failure: I. The Effect of Edema on Oxygen Utilization, *J. Clin. Investigation* 8:259-290, 1930.

In my opinion, this functional inefficiency in the exchange of gases and electrolytes between tissue cell and capillary blood stream due to abnormal accumulations of interstitial fluid secondary to capillary hypertension necessitated by increased venous pressure due to incompetent venous valves is the reason for the heaviness, the edema, the easy fatigability and the increased susceptibility to infection and trauma which are so distressing to the patient with varicose veins. I do not believe that differences in the concentration of carbon dioxide and oxygen which may exist between the normal cubital vein and the varicose long saphenous vein in the same patient<sup>29</sup> are responsible for the patient's complaints. Blalock<sup>30</sup> observed that although in general the carbon dioxide content was higher and the oxygen content was lower in blood from uncomplicated varicose veins than in that from normal veins, in the presence of varicose ulceration (with which interference with nutrition is most marked) the findings were reversed, i. e. the venous blood contained more oxygen and less carbon dioxide than the blood in normal veins. Again, the magnitude of the changes in carbon dioxide and oxygen concentrations in varicose veins is insignificant in comparison with those found in normal veins during even mild exercise (70.6 volumes per cent carbon dioxide).<sup>23b</sup>

This hypothesis finds ample confirmation in the clinic. Patients with asymptomatic superficial varices are not uncommon, and in each instance careful examination will reveal normal deep and communicating veins, i. e. an alternate normal route for venous return. In patients with severe symptoms, especially with varicose ulceration, the converse is true, i. e. either deep or communicating veins are incompetent also. That this may be a single incompetent communicating vein directly beneath an ulcer was demonstrated time and again several years ago, when a common form of treatment for patients with varicose ulceration was excision and skin grafting.

If varicose ulceration is taken as an index of the degree of physiologic interference, the comparison between patients in whom only the superficial veins are incompetent and those in whom either the deep or the communicating veins are incompetent also is striking.

Among patients with superficial varices associated with incompetence of the long or short saphenous veins, varicose ulceration is rare. Of patients with superficial varices associated with incompetence of communicating veins in the lower leg, 86 per cent had or had had varicose

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29. (a) Linton, R. R.: The Communicating Veins of the Lower Leg and the Operative Technic for Their Ligation, *Ann. Surg.* **107**:582-593, 1938. (b) Edwards.<sup>8</sup> (c) de Takáts, Quint, Tillotson and Crittenden.<sup>11c</sup>

30. Blalock, A.: Oxygen Content of Blood in Patients with Varicose Veins, *Arch. Surg.* **19**:898-905 (Nov.) 1929.

ulceration.<sup>14</sup> In patients with incompetence of the long saphenous vein, retrograde blood can be eliminated by ligation of this vein at the sapheno-femoral junction. Following this combined with injection therapy, complete relief is to be anticipated. In patients with incompetence of the deep or the communicating veins in the lower leg, however, this is not so readily accomplished. The physiologic impairment is much greater (for example, Holling and Beecher<sup>31</sup> found that fluid accumulated at twice the normal rate in patients with incompetent deep or communicating veins; in patients with the superficial veins alone incompetent, the rate was normal). The elimination of this localized congestive failure is not easy. In approximately 5 per cent of patients of this type there is obstruction to venous return in the deep veins, as demonstrated by Perthes' test,<sup>32</sup> so that obliteration of superficial varices is unwise. In these patients the superficial varicosities are compensatory, and their treatment not only does not help the patient but is definitely harmful. It is fortunate, however, that in patients of this type with the passage of time, it is not uncommon for the deep veins to become sufficiently patent or for sufficient deep collateral channels to develop to permit more active treatment. Where deep channels are adequate, surgical interruption of incompetent communicating veins following the technic of Linton<sup>29a</sup> is usually desirable.

This is definitely a major operation and requires prolonged hospitalization. It should be preceded by ligation of both the long and short saphenous veins to prevent possible blood stream infection or pulmonary embolus. In my hands, even such extensive operation has proved no guarantee against recurrence and follow-up visits and supplementary treatment at frequent intervals are of the utmost importance. In many instances the loss of tone of the subcutaneous tissues is such that the prolonged application of external elastic compression, either with elastic bandages or with an elastic stocking, may be desirable. When the patient's work requires a great deal of standing, a change of occupation may be necessary.<sup>33</sup>

#### CONCLUSIONS

In varicose veins venous valves become incompetent and assist in venous return only with difficulty.

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31. Holling, H. H.; Beecher, H. K., and Linton, R. R.: Study of Tendency to Edema Formation Associated with Incompetence of Valves of Communicating Veins of the Leg, *J. Clin. Investigation* **17**:555-561, 1938

32. von Perthes, G.: Ueber die Operation der Unterschenkelvaricen nach Trendelenburg, *Deutsche med. Wchnschr* **21**:253-259, 1895.

33. Eyster, J. A. E.: Venous Pressure and Its Clinical Application, *Physiol. Rev.* **6**:281, 1926. Turner, A. H.; Newton, M. I., and Haynes, F. W.: The Circulatory Reaction to Gravity in Healthy Women, *Am. J. Physiol.* **94**:507-520. 1930. Harrop and Waterfield.<sup>11f</sup>



This interference with the normal mechanism of venous return is reflected by increased venous pressure.

This increased venous pressure is not of great significance so long as there is an alternate normal route (deep and communicating veins) for the return of blood from the capillaries to the heart.

When no such normal route persists, increased venous pressure provokes increased capillary pressure, which, in turn, is followed by increased interstitial fluid and interference with the exchange of gases and metabolites between tissue cell and capillary blood stream.

Lasting cure of patients with varicose veins has been experienced only when physiologic abnormalities have been corrected or compensated. Obliteration of the superficial varices alone has rarely proved of more than temporary benefit to patients with incompetence of large venous trunks.

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# MESENTERIC VASCULAR OCCLUSION

REVIEW OF THE LITERATURE AND GENERAL PRINCIPLES; REPORT  
OF A CASE WITH OPERATION AND RECOVERY

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AND

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Occlusion of the mesenteric vessels is not the rare occurrence of years ago, for today practically every busy surgeon encounters 1 or more cases. Although the underlying pathologic lesions appear to be many, the resulting clinical picture is fairly characteristic and makes possible an early and definite diagnosis in the majority of cases. The mortality rate associated with mesenteric vascular occlusion is still high and can be reduced only by earlier diagnosis and treatment. Whittaker and Pemberton,<sup>1</sup> reporting 19 cases as late as 1938, had a mortality rate of 84 per cent following surgical intervention. The lowest recorded mortality rate in any significant series is in the region of 60 per cent.

The history of mesenteric occlusion is about a hundred years old, for Tiedemann<sup>2</sup> reported the first case in 1843. Virchow was the first to recognize and explain embolism and thrombosis, and the knowledge of these processes as they occur in the mesenteric vessels dates from the publication of his admirable investigations. He reported 1 case of mesenteric occlusion in 1847<sup>3</sup> and seven years later followed with 2 more.<sup>4</sup> In 1875 Litten<sup>5</sup> summarized the 20 cases reported until then. However, it was not until 1895 that Elliot<sup>6</sup> performed the first intestinal

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From Grace Hospital.

1. Whittaker, L. D., and Pemberton, J. de J.: Mesenteric Vascular Occlusion, *J. A. M. A.* **111**:21 (July 2) 1938.

2. Tiedemann, F.: Von der Verengerung und Schliessung der Pulsadern in Krankheiten, Leipzig, K. Gross, 1843, p. 131.

3. Virchow, R.: Ueber die akute Entzündung der Arterien, *Virchows Arch. f. path. Anat.* **1**:272, 1847.

4. Virchow, R.: Verstopfung der Gekrösarterie durch einem ungewanderten Propf, *Verhandl. d. phys.-med. Gesellsch. in Würzburg* **4**:341, 1854.

5. Litten, M.: Ueber die Folgen des Verschlusses der Arteria mesaraica superior, *Virchows Arch. f. path. Anat.* **63**:289, 1875.

6. Elliot, J. W.: The Operative Relief of Gangrene of the Intestine Due to Occlusion of the Mesenteric Vessels, *Ann. Surg.* **21**:9-23, 1895.

resection in the treatment of this disease. Gordon<sup>7</sup> and then Tyson<sup>8</sup> soon followed with reports of operative recoveries. Watson<sup>9</sup> at the turn of the century reported that resection was a suitable procedure in about one sixth of the cases. Sporadic reports quickly followed, and experimental study to determine the mechanism of the lesion was begun. In 1904 Jackson, Porter and Quinby<sup>10</sup> reviewed the 214 cases recorded up to that time. Trotter,<sup>11</sup> in 1913, in his excellent monograph reported 359 cases collected from the literature and described 7 cases of his own. In 1921 Klein<sup>12</sup> conducted an exhaustive review and found that only 24 cases of successful resection had been reported. In 1923 Brady<sup>13</sup> reported 14 cases. In 1926 Cokkinis<sup>14</sup> reviewed 76 cases collected from the London hospitals and recorded some original research on mesenteric circulation. The more recent reviews of series of cases were presented by Meyer,<sup>15</sup> Jones,<sup>16</sup> Dye,<sup>17</sup> Warren and Eberhard,<sup>18</sup> Whittaker and Pemberton<sup>1</sup> and Fallis,<sup>19</sup> and in 1941 Moore<sup>20</sup> reviewed the history and reported 8 of his own cases.

The anatomy of the mesenteric vessels has been carefully worked out, so that the main vessels, branches, arterial arcades and anastomoses

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7. Gordon, T. E.: *Brit. M. J.* **2**:1447, 1898.

8. Tyson, W. J., and Linington, W. W.: Case of Acute Intestinal Obstruction Due to Embolus of a Branch of Superior Mesenteric Artery, *Tr. Clin. Soc. London* **35**:114-116, 1901-1902.

9. Watson, F. S.: *Diagnosis and Surgical Treatment of Embolism and Thrombosis of the Mesenteric Blood Vessels, with Reports of Cases*, Boston M. & S. J. **132**:552-557, 1894.

10. Jackson, J. M.; Porter, C. N., and Quinby, W. C.: Mesenteric Embolism and Thrombosis: A Study of Two Hundred and Fourteen Cases, *J. A. M. A.* **42**:1469 (June 4) 1904; **43**:25 (July 2); 110 (July 9); 183 (July 16) 1904.

11. Trotter, L. B. C.: *Embolism and Thrombosis of Mesenteric Vessels*, London, Cambridge University Press, 1913.

12. Klein, E.: *Embolism and Thrombosis of the Superior Mesenteric Artery*, *Surg., Gynec. & Obst.* **33**:385, 1921.

13. Brady, L.: Mesenteric Vascular Occlusion, *Arch. Surg.* **6**:151 (Jan.) 1923.

14. Cokkinis, A. J.: *Mesenteric Vascular Occlusion*, Baltimore, William Wood & Company, 1926.

15. Meyer, J. L.: Mesenteric Vascular Occlusion, *Ann. Surg.* **94**:88-96 (July) 1931.

16. Jones, H. W.: Recurring Mesenteric Thrombosis, *Am. J. Surg.* **22**:318-320 (Nov.) 1933.

17. Dye, W. J. P.: Mesenteric Thrombosis, *New England J. Med.* **212**:105-108 (Jan. 17) 1935.

18. Warren, S., and Eberhard, T. P.: Mesenteric Venous Thrombosis, *Surg., Gynec. & Obst.* **61**:102-121 (July) 1935.

19. Fallis, J.: Mesenteric Thrombosis—Operation—Recovery: Report of Two Cases, *Am. J. Surg.* **47**:128 (Jan.) 1940.

20. Moore, T.: Mesenteric Vascular Occlusion, *Brit. J. Surg.* **28**:347 (Jan.) 1941.

are well known. The venous drainage of the large and the small bowel for the most part is patterned after the arterial supply.

Donaldson and Stout<sup>21</sup> contributed to the pathology of this disease and by their careful clinical observations and animal experimentations differentiated between arterial and venous occlusion of the mesenteric vessels. They pointed out that with venous thrombosis the muscular structure of the intestinal wall remains viable for a considerable time, whereas with arterial thrombosis gangrene of the intestinal wall comes on almost immediately. Although it was believed at first that the majority of mesenteric vascular occlusions were on the basis of the arterial embolism, the latest series of cases indicate that venous obstruction accounts for about 75 per cent of the cases and that the terminal mesenteric arteries are secondarily involved.

From the literature one can evolve a simple working classification of mesenteric vascular occlusion. The occlusion may be: (1) arterial, in which embolism or thrombosis has occurred, and this may be general, i. e. with diffuse infarction, or local, i. e. with segmental infarction, or (2) venous. The series of cases reported have shown that the causative factors are many and various. The arterial type is due to embolism or thrombosis. The embolic group appears to be the larger, and as early as 1900 it was noted that the superior mesenteric artery was involved many times more frequently than the inferior mesenteric artery. This fact can be explained on the basis of earlier exit from the aorta and also on the basis of the superior mesenteric artery being more of a direct continuation from the abdominal aorta. Vegetations on the valves on the left side of the heart and auricular fibrillation appear to be the usual causative agents in embolism of the mesenteric arteries. Thrombosis of the arteries is due to arteriosclerosis or atherosclerosis or to pressure on the wall of the vessel, as from tumor. Venous occlusion appears to be due almost always to thrombosis; the concept of retrograde venous embolism has few supporters. Mesenteric venous thrombosis is usually associated with infection in the abdominal organs that are tributary to the portal vein. Appendicitis, diverticulitis, ulcerative colitis, pelvic infections, carcinoma and strangulated bowel are frequent precursors of this condition. Thrombosis or embolism of mesenteric vessels rarely affects children; adults 40 to 65 years of age form the group most frequently attacked. In 1901 Taylor<sup>22</sup> reported occlusion of the superior mesenteric artery and vein in a girl at the unusual age of 5 years.

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21. Donaldson, J. K., and Stout, B. F.: Mesenteric Thrombosis: Arterial and Venous Types as Separate Clinical Entities; Clinical and Experimental Study, *Am. J. Surg.* **29**:208 (Aug.) 1935.

22. Taylor, F.: *Tr. Path. Soc. London* **32**:61, 1901.

Review of the more constant clinical features reveals that there usually is a sudden onset of severe central abdominal pain, which in about 50 per cent of the cases tends to become colicky. Vomiting is marked from the onset. Shock is usually present, the degree varying with the type of occlusion. Constipation is present. Later, all the symptoms of intestinal obstruction supervene. Of late it has been shown that the vomiting is markedly overshadowed by the severe pain; the reverse of this is true in practically all other types of intestinal obstruction. On examination the patient is usually found to be a dehydrated person in a varying degree of shock with generalized abdominal tenderness, spasm and rigidity. Occasionally, thickened coils of intestine may be palpated. Rectal examination often reveals blood on the examining finger. In a questionable case a low easy enema often yields a return of blood-stained fluid; this has been considered to be a diagnostic point. The white blood cell count is apt to be between 25,000 and 40,000. The most common mistaken diagnoses have been acute hemorrhagic pancreatitis, perforated peptic ulcer and acute cholecystitis.

Moore urged abdominal exploration as soon as the patient can be made as safe as possible for operation. Boyce and McFetridge<sup>23</sup> applied the dictum that the most hopeful thing about mesenteric thrombosis is that it can be cured by operation. Of course, surgical intervention is more urgently required in cases of the arterial type. Moore stated that the mortality rate without operation in cases of occlusion of the superior mesenteric artery is 100 per cent. He described some of the occasional cases of recovery without operation reported in the literature<sup>24</sup> as examples of thrombosis of the superior mesenteric vein and others as instances of local arterial occlusion in which the collateral circulation has been sufficient to sustain the life of the affected bowel.

Excision of the affected bowel and mesentery has been advised even in desperate cases. The bowel ends should be closed and side to side anastomosis performed. Exteriorization of the bowel has been fatal in practically all cases in which this was done. Only in the occasional case in which the colon alone was involved did exteriorization prove beneficial.

#### REPORT OF CASE

T. M., a 38 year old white Italian man, entered Grace Hospital with the complaint of pain in the left lower quadrant of the abdomen of fourteen hours' duration.

Three months previously this patient had entered the hospital with an acute condition within the abdomen requiring operation. Through an upper right rectus

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23. Boyce, F. F., and McFetridge, E. M.: Mesenteric Vascular Occlusion, *Internat. S. Digest* 20:67 (Aug.) 1935.

24. Sargent, R. M.: Spontaneous Recovery in Superior Mesenteric Thrombosis, *Brit. M. J.* 2:64 (July 14) 1934.

incision the abdomen was entered, and a perforated duodenal ulcer was noted. The perforated ulcer was plicated, and the abdomen was then closed in the usual fashion, the upper quadrant being drained with two eiqaret drains. The patient was discharged from the hospital on the seventeenth postoperative day after a stormy convalescence, during which acute pulmonary edema and acute pneumonitis developed. However, after discharge he remained perfectly well, being subjected to a strict convalescent regimen for ulcer. On the night before his second admission to the hospital sharp pains localized to the left lower quadrant of the abdomen developed. The pains were associated with nausea and three episodes of vomiting; there was no blood in the vomitus. The pain did not radiate, remained moderately severe and did not seem to be affected by anything the patient did. He had had no bowel movement since the onset of the pain. There were no other symptoms. The past history was otherwise not pertinent, and the familial history was noncontributory.

Physical examination revealed a well developed and fairly well nourished white man complaining of severe pain in the left lower quadrant of the abdomen. The heart and the lungs were normal. The blood pressure was 104 systolic and 50 diastolic. The abdomen was moderately distended and tympanitic throughout except in the left lower quadrant, where it was dull. There was generalized tenderness, most marked in the left lower quadrant; here there were muscle spasm and an ill defined mass. Rectal examination revealed no abnormalities.

The rectal temperature was 99.6 F. The pulse rate was 80. The respiration rate was 20.

The blood showed a red cell count of 5,300,000 with 70 per cent hemoglobin and a white cell count of 15,800 with 84 per cent polymorphonuclears.

The patient was operated on soon after admission with a preoperative diagnosis of intestinal obstruction and probably mesenteric thrombosis. With the patient under spinal anesthesia induced with pontocaine hydrochloride the abdomen was opened through a lower left rectus incision. A large amount of bloody fluid was found in the peritoneal cavity. This was suctioned out, and in the middle and left lower quadrants of the abdomen there was a loop of ileum (middle portion of the ileum), which was hyperemic, congested, edematous and rigid. The extent of involvement was about 12 inches (30.5 cm.), and the mesentery in this area was hemorrhagic and thickened. The involved portion of the bowel (12 inches) and the mesentery was resected, and end to end anastomosis was performed. The patient withstood the procedure well and was returned to his room in a fair condition.

His postoperative convalescence was remarkably smooth, and he was discharged from the hospital with the prescription of a convalescent diet for ulcer on the sixteenth postoperative day.

The pathologist's report stated that grossly the specimen consisted of a purplish red hemorrhagic portion of intestine the attached mesentery of which was markedly infiltrated with blood. At each end the intestine was lighter in color than in the middle portion. Sections of the mesentery showed the tissue much infiltrated with blood and thrombotic masses filling the lumen of the venous channels. The walls of the veins showed considerable cellular infiltration.

Two months after the patient was discharged from the hospital, a complete gastrointestinal series of roentgenograms was taken. No abnormalities other than prepyloric and duodenal ulcers were seen. The patient was seen again four and seven months after operation. He had no complaints and had resumed his previous occupation, that of a baker in a restaurant.

## COMMENT

This case clinically and pathologically is one of venous mesenteric occlusion. Typically, the onset was moderate rather than sudden as in the collapse of arterial occlusion. The patient hospitalized early and subjected to early exploratory operation already showed moderately advanced changes in the intestine and the mesentery. The fact that only 12 inches of ileum had to be resected is in line with the present accepted teaching that the thrombotic process begins in the peripheral branches of the mesenteric veins, i. e. in those portions of the vessels situated either close to or actually in the intestinal wall, and that from this point the process extends in an ascending fashion.

With regard to the cause of the thrombosis in this case one can only conjecture. Just what part the operation of three months before (for ruptured peptic ulcer) played is interesting to consider. Certainly, one must also consider the element of inflammation or infarction, for the venous walls showed marked cellular infiltration, the picture of thrombophlebitis.

The response to the question "Why did this patient survive when so many others do not?" is based on several factors: 1. The occlusion was on the venous rather than on the arterial side. 2. The patient was operated on early, before the thrombotic process had ascended. 3. The operation performed was the least shocking and the most rapid procedure. 4. The postoperative care was carefully planned and carried out. 5. The patient had no other severe complicating disease.

## SUMMARY AND CONCLUSIONS

The literature and the general principles of mesenteric vascular occlusion are reviewed.

A case with operation and cure is reported.

It is hoped that with earlier diagnosis, earlier operation and the newer aids of heparin and papaverine hydrochloride that the mortality rate will be substantially reduced in the near future.

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# PROGRESS IN ORTHOPEDIC SURGERY FOR 1941

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE  
AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

(Continued from Page 506)

## III. CONGENITAL DEFORMITIES

*Experimental.*—The occurrence of skeletal abnormalities in the offspring of rats reared on a deficient diet is reported on by Warkany and Nelson.<sup>116</sup> They fed albino rats of the Sprague-Dawley strain which were entirely free of abnormalities a diet composed of yellow corn meal (76 per cent), wheat gluten (20 per cent), calcium carbonate (3 per cent) and sodium chloride (1 per cent) with sufficient viosterol. Multiple skeletal abnormalities appeared in the offspring. These consisted of shortening or absence of the tibia, the fibula, the radius, the ulna and the bones of the hands and the hind feet; shortening of the mandible; fusion of the ribs, and various deformities of the sternum, the maxilla, the clavicle and the scapula. These abnormalities were not present if pig liver (2 per cent) was added to the diet. [ED. NOTE: One of us (J. H. K.) has had the pleasure of examining the cleared specimens and studying the pictures of these abnormalities. This seems to be an important contribution to the study of congenital deformities. For some years this editor has observed the large percentage of cases of congenital clubfoot occurring in poor families and has thought that maybe their diets lacked some factor which was necessary to stimulate the proper development of the embryo at the proper time and that failing this stimulus the foot did not develop normally. This editor has been unable clinically to find anything to substantiate this idea. While none of these rat embryos showed clubfoot, they did show most of the other common congenital deformities.]

*Arachnodactylia.*—Ellis,<sup>120</sup> in reporting arachnodactylia and ectopia lentis in father and daughter, says:

For many years after the original description of "dolichosténomélie" by Marfan (1896), this particular type of local gigantism of the extremities received little general recognition until Ormond (1924, 1929) drew the attention of ophthalmologists to the frequent association of the skeletal deformities with congenital

116. Warkany, J., and Nelson, R. C.: Skeletal Abnormalities in Offspring of Rats Reared on Deficient Diets, *Anat. Rec.* **79**:83-100 (Jan. 25) 1941.

117-119. Footnotes deleted.

120. Ellis, R. W. B.: Arachnodactylia and Ectopia Lentis in Father and Daughter, *Arch. Dis. Childhood* **15**:267-273 (Dec.) 1940.



dislocation of the lenses. . . . As the name arachnodactyly (Achard, 1902) [spider fingers] implies, the most striking feature of the condition is usually the extreme length and slenderness of the digits.

Sometimes the arms and legs are involved without the hands and feet. The patients are tall and slender and may have scoliosis, kyphosis or pigeon breast.

. . . Laxity of the ligaments tends to make the patients clumsy and graceless, whilst deformities of the feet (pes planus, hammer-toe) are the general rule. Other bony abnormalities such as spina bifida . . . have been described, whilst in three instances . . . arachnodactyly has been associated with fragilitas ossium and blue sclerotics. . . . Radiologically the bones of the extremities, particularly the phalanges, metacarpals and metatarsals, show the extreme length and slenderness observed clinically. Ossification is usually normal for age; extra epiphyses have been described in the digits, but these do not appear to be the rule. . . . In about two-thirds of the cases the skull is dolichocephalic. . . . Congenital morbus cordis occurs sufficiently often (in one-third or more of the cases) to be regarded as an integral part of the complete syndrome.

Many other additional congenital abnormalities have been described, either in association with arachnodactylia or occurring in other members of affected families. Some degree of webbing of the fingers is common; the ears are often prominent or malformed, and the musculature is poorly developed. There is congenital dislocation of the lenses.

Dax,<sup>121</sup> in an article on arachnodactylia, says:

. . . The appearance of these cases is unmistakable, and although arachnodactyly is a picturesque description for the hands and feet, it does not convey the impression of general skeletal disproportion as does Marfan's term [dolichosténomélie—long narrow limbs]. The slender fingers are sometimes webbed, the long toes may show a hammer deformity and spurring of the os calcis is described. The thorax is long, flat, narrow and funnel-shaped, there is usually a kyphoscoliosis due to an elongation of the vertebral column and there is winging of the scapulae.

The skull is dolichocephalic, the nose long and prominent, and the palate arched and high. The ears are long and abnormally formed. There may be facial asymmetry. There is a loss of subcutaneous fat, the ligaments are lax and the muscles are thin and hypotonic; flat feet and spontaneous subluxations of the joints are seen in consequence. . . .

Four cases of arachnodactyly are described in mental defectives. Two are associated with retinitis pigmentosa and a third with juvenile amaurotic idiocy. A comparison is made between arachnodactyly and chondrodystrophy.

Numerous reports of arachnodactylia associated with ectopia lentis have been published. Meyer and Holstein<sup>122</sup> say that it is still a debatable question whether there is a relation between lens anomalies

121. Dax, E. C.: Arachnodactyly, *J. Ment. Sc.* **87**:434-438 (July) 1941.

122. Meyer, S. J., and Holstein, T.: Spherophakia with Glaucoma and Brachydactyly, *Am. J. Ophth.* **24**:247-257 (March) 1941.

and muscular-skeletal changes. They are able to demonstrate in another form of lens anomaly, namely, microphakia, that in other parts of the body similar changes occur that are significant enough to reveal a definite relation between lens and constitutional anomalies.

*Ehlers-Danlos Syndrome.*—Pittinos<sup>123</sup> reports a case of Ehlers-Danlos syndrome. This syndrome was first described by Ehlers in 1899 before the Danish Dermatological Society. It shows three distinguishing features: (1) fragility of the skin and the blood vessels (dermatorrhesis); (2) overelasticity of the skin (dermatocholasia), and (3) overelasticity of the joints (arthrocholasia). In some instances additional evidence of pseudotumors and subcutaneous nodules has been noted. The former occur in places of repeated trauma, such as over the achilles tendon, and are thought to be due to repeated extravasation of blood. The latter are due to small areas of fat necrosis in subcutaneous tissue. The outstanding feature in the case he reports was weakness with an increased output of creatine but no definite muscular dystrophy.

Barber, Fiddes and Benians,<sup>124</sup> in an article on Ehlers-Danlos syndrome, state that it was nine years after Ehlers had presented his case for diagnosis in Denmark that Danlos (1908) recognized the similarity between Ehlers' patients and a patient described eighteen months before as having a doubtful form of diabetic xanthomatosis. Danlos noted the hyperelasticity of the skin, its remarkable thinness and the abnormal cicatricial effects following wounds.

Barber, Fiddes and Benians think the basis is probably a developmental error. They present a case in which there was synostosis of the proximal heads of the radius and the ulna on both sides. In some cases there may be an absence or delay of cranial ossification. In two families it was possible to trace some manifestation of the syndrome through several generations. The authors say:

. . . The principal clinical features remain the triad of signs first described by Ehlers—over-extensibility of the joints with hyperelasticity and fragility of the skin. . . . [The skin] is found to slide easily over the subcutaneous tissues, whether muscle or bone, and in this respect has been likened not inaptly to the skin of a cat or a dog. . . . It may be pulled out to a considerable extent, resuming its original position when released. Surprisingly little discomfort is caused by pinching the skin, which nevertheless appears to be unduly sensitive to other more usual manipulations. . . . The numerous large atrophic scars on the exposed portions of the body testify to the third feature of the triad—the fragility of the skin. The smallest injury will produce a bruise and such haematomas are frequently extensive. . . . On healing, the wounds leave broad papyraceous scars. . . . These scars are never adherent to the subcutaneous tissues. . . . Where the skin is normally fairly loose, as over the

123. Pittinos, G. E.: Ehlers-Danlos Syndrome with Disturbance of Creatine Metabolism: Report of a Case, *J. Pediat.* **19**:85-89 (July) 1941.

124. Barber, H. S.; Fiddes, J., and Benians, T. H. C.: Syndrome of Ehlers-Danlos, *Brit. J. Dermat.* **53**:97-112 (April) 1941.

elbows and knees, large sponge-like blue-gray tumours sometimes develop in the scars. . . . The degree of over-extensibility of the joints varies from looseness of the first metacarpo-phalangeal articulation to spontaneous subluxation of the larger joints.

An additional sign is the presence of freely movable nodules under the skin. These spherules have been several times described as lipomas. Their presence has been considered a fifth diagnostic sign.

The fourth sign consists of the presence of pseudotumors. They are of two types, and both types are due to trauma. In 1 case there was an inflammatory granuloma with giant cells. (There is a long histologic description of the second type of tumor.)

Launay<sup>125</sup> reported the Ehlers-Danlos syndrome in an 11 year old boy who showed mental retardation.

*Gargoylism.*—Henderson<sup>126</sup> reports 5 cases, and Ellis<sup>127</sup> reports 1 case of this rare familial syndrome called gargoylism. The name was given by Ellis in 1936. Briefly, the disease is a form of congenital chondro-osteodystrophy in which the deformities of the head, the trunk and the limbs are associated with mental defect, corneal clouding and hepatosplenomegaly.

In describing the head Henderson says the grotesque facial appearance is typical and one of the most constant features of the disease. The nasal bridge is flat and wide, and the nostrils are often turned forward. The mandible is frequently broad and heavy, and the teeth are widely spaced, irregular and poorly developed. Dentition commenced at the normal time in about half of the cases but in others was greatly delayed. The lips are usually thick, and the large tongue, often fissured, lies well forward in a slightly open mouth, sometimes actually protruding a little. Full cheeks are the rule, and they often have a ruddy hue. The ears usually appear to be unduly low set and occasionally are enlarged. Coarse dark eyebrows frequently add to the uncanny appearance, but the hair is usually fine and silky. The neck is short, the head appearing to be flattened on the shoulders. The chest is seldom well formed, but gross malformations such as occur in cases of Morquio's disease have not been observed. Roentgenograms show considerable broadening of the ribs. Dorsolumbar kyphosis is seldom absent and is caused by dysplasia of one or more of the upper lumbar vertebrae. The affected vertebrae are notably small, with a flattened or wedge-shaped body which frequently bears an anterior hoodlike process. The most conspicuous features are the relatively

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125. Launay, C.: Ehlers-Danlos Syndrome Associated with Mental Retardation in Boy Eleven Years Old, *Bull. et mém. Soc. méd. d. hôp. de Paris* **65**:709-711 (Jan. 6) 1941.

126. Henderson, J. L.: Gargoylism: Review of Principal Features with Report of Five Cases, *Arch. Dis. Childhood* **15**:201-214 (Dec.) 1940.

127. Ellis, R. W. B.: Report of Additional Case of Gargoylism, *Arch. Dis. Childhood* **15**:215-218 (Dec.) 1940.

short arms and impaired mobility of the joints with slight permanent semiflexion. This impaired movement gives these patients an ungainly and sometimes a slightly crouching attitude and a stiff clumsy gait. The scapulas usually lie abnormally high, and Engle has stated that Sprengel's deformity is a characteristic feature of the syndrome. Movement at the shoulder is restricted on abduction of the arms, the scapulas being rotated into the axillas. The broad short clawhands are conspicuous. In the hips and the lower extremities coxa valga, genu valgum and pes planus have been observed on several occasions.

The roentgenologic changes are more striking in the limbs than elsewhere. The bones are thickened and roughly formed; the roughness of formation is most apparent in the neighborhood of joints. The humeral and femoral heads are irregular and flattened and the glenoid fossae and the acetabulums unduly shallow. Irregular epiphysial ossification is a constant feature, osteosclerotic and rarefied patches often being seen. Carpal ossification is retarded. The mental defect of amenia is one of the most characteristic features of the disease; most of the patients were affected. Corneal clouding is another salient feature. Hepatosplenomegaly occurs in a majority of cases. Several writers express the opinion that gargoylism should be grouped with the lipoidosis. Henderson states:

. . . The other diseases comprising this group are Gaucher's disease, Schüller-Christian's disease, Niemann-Pick's disease and Tay-Sach's disease. In all five conditions the familial incidence is significantly high and it would seem that all are recessively inherited. Further, although some cases of Gaucher's disease and Schüller-Christian's disease may not become manifest until adult life, they all predominate in early childhood and are essentially congenital.

In summary he writes:

The disease is congenital, and the principal clinical features are chondro-osteodystrophy with extreme dwarfism, mental defect, corneal clouding and hepatosplenomegaly.

The most constant pathological changes are found in the osseous and nervous systems. The bones are thickened and many of them display characteristic deformities. In the brain there are widespread degenerative changes in the nerve cells with intra- and extracellular lipoid deposits. Lipoid deposits may occur in the corneae, liver, spleen and other tissues.

The disease is recessively inherited, and there is a high familial incidence. There have been 5 instances of consanguinity in the parents.

*Ectodermal Dysplasia.*—Friedman<sup>128</sup> adds the forty-fifth case of an interesting condition to the literature. He says:

Hereditary ectodermal dysplasia of the anhidrotic type is an entity which presents a typical, conspicuous and easily recognizable clinical picture. It has, among others, a pathognomonic quartet of symptoms: *First*, complete absence of

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\* 128. Friedman, R.: Hereditary Ectodermal Dysplasia of Anhidrotic Type, Urol. & Cutan. Rev. 44:464-468 (July) 1940.

sudoriparous glands, the direct consequence of which is an inability to sweat (anhidrosis) and to withstand heat. *Second*, a deficiency of the sebaceous glands and hair of the scalp, axillary and pubic regions. With this is associated an absence of the pilosebaceous apparatus elsewhere on the body (asteatosis and hypotrichosis). *Third*, a partial and sometimes even a total absence of teeth (anodontia). Teeth when present exhibit a characteristically incomplete development. *Fourth*, a pronounced tendency for hereditary transmission, usually through the female to the male.

In 1929 Weech suggested the term "hereditary ectodermal dysplasia of the anhidrotic type," which has been used by more than half of the authors since that time.

The patient whose case Friedman reports had spina bifida, no coccygeal segment and retardation of development of the maxilla, the carpal and the tarsal bones. The conic tapering of the fingers was also present in the mother and a maternal uncle.

*Absence of Nails.*—Jacoby, Ripman and Munden<sup>129</sup> report the case of a 2½ year old girl who had swollen gums and only two lower incisor teeth. The nails were completely absent from part of the fingers and the toes. There was precocious development of the epiphyses so that the bones resembled those of a child 4 to 6 years of age. They conclude that

. . . the condition of the nail may be closely correlated with the condition of the underlying terminal phalanx, in that where the nail is absent or rudimentary, the terminal phalanx is also absent or rudimentary.

*Klippel-Feil Syndrome.*—Gilmour<sup>130</sup> discusses the essential identity of the Klippel-Feil syndrome and iniencephaly. He says:

The *Klippel-Feil syndrome* or congenital brevicollis consists of shortness of the neck, a low hair-line posteriorly and limitation of movements of the head, associated with fusion of cervical vertebrae and sometimes also of the upper thoracic vertebrae. . . . [Additional features are] webbing of the neck (pterygium colli) due to an unusual prominence of the free borders of the trapezius muscles, marked nuchal depression at the nape of the neck, congenital high scapula, winged scapula, facial asymmetry, spasm of the cervical muscles or torticollis. cervical ribs, absence or fusion of the ribs, scoliosis and dorsal kyphosis. Less common congenital abnormalities are spina bifida in the lumbar or sacral region, sacralisation of the fifth lumbar vertebra, cleft palate or abnormalities of the viscera. . . .

*Iniencephaly* [a condition in which the fetus has a fissured occiput and a protruding brain] is a deformity found only in the stillborn or in infants. One infant in the literature lived for 39 hours. This is probably about as long a

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129. Jacoby, N. M.; Ripman, H. A., and Munden, J. M.: Partial Anonychia (Recessive) with Hypertrophy of Gums and Multiple Abnormalities of Osseous System: Report of a Case, *Guy's Hosp. Rep.* 90:34-40, 1940-1941.

130. Gilmour, J. R.: Essential Identity of Klippel-Feil Syndrome and Iniencephaly, *J. Path. & Bact.* 53:117-131 (July) 1941.

post-foetal life as the deformity would ever permit. Most infants are born prematurely; some of the stillborns are macerated, others fresh. The great majority are females. In 35 cases to which I have referred 32 were females and 3 males. The deformity is very characteristic. . . . There is great retroflexion of the head so that the face looks upwards and forwards. The head is commonly enlarged. The neck is absent or only indicated anteriorly below the chin. The scalp becomes continuous with the skin of the lower part of the back, perhaps as far down as the sacral region. The skin of the face usually passes directly on to that of the chest. The scapulas are pushed aside by the head and are laterally situated. The shoulders become more anterior than normally. The bony abnormality is in the occiput, the cervical spinal column and a variable length of the spine below this. In many cases there is an encephalocele at the back of the head where it joins the back, and there may be a defect in the skin covering it. . . .

After reporting a case of each condition he summarizes:

An example of the Klippel-Feil syndrome and of iniencephaly are described, with a detailed report of the bony deformities found at necropsy in each. From the similarity of the changes in these two cases and in cases in the literature described under one or other name it is concluded that the Klippel-Feil deformity is a mild form of the deformity characteristic of iniencephaly.

*Elevation of the Scapula.*—Smith<sup>131</sup> makes a thorough review of congenital elevation of the scapula. He recalls that the upper limb bud develops as a mass of undifferentiated mesoderm in the cervical region during the fourth week of fetal life. Early in the fifth week the condensation of the scleroblastema of the bud has extended to the distal part, and the anlagen of the scapula, the humerus, the radius and the ulna are distinguishable. The scapula migrates downward from the level of the fourth cervical vertebra to its usual position by the end of the third month. This happens at a time when external influences would have little effect on the descent of the scapula. There is often a connection between the scapula and the cervical portion of the spine. The author discusses the significance of the omovertebral bone in terms of comparative anatomy.

The physical findings in 50 cases of congenital high scapula, including associated deformities, are given. The results of 13 operations of various types for congenital elevation of the scapula are described. An increase in abduction of the shoulder was obtained in 3 cases by removal of an omovertebral bone. Attempts to improve the appearance of the shoulder by resection of a large portion of the scapula were disappointing. In 3 of 5 cases radical freeing of the scapula and suturing it to one of the lower ribs resulted in cosmetic and functional improvement.

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131. Smith, A. DeF.: Congenital Elevation of Scapula, Arch. Surg. **42**:529-536 (March) 1941.

The author concludes that congenital elevation of the scapula is the result of a true defect in the embryo. The omovertebral structure which occurs in about 25 per cent of these cases is a homologue of the supra-scapular bone which is found in several of the lower vertebrates. In many cases of congenital elevation of the scapula the cosmetic and functional defects are not of sufficient severity to warrant any operation. In cases in which an omovertebral bone is associated with marked limitation of abduction at the shoulder, improvement in function may be obtained by removal of the bone. In certain cases of marked elevation of the scapula, improvement in appearance and function may be had by extensive subperiosteal release of the scapula and retention of the bone in a lower position by suturing it to a rib. The operation is fraught with difficulty, however, and the result may be impaired by several complications.

Hadley<sup>132</sup> reviews the literature on Sprengel's deformity and reports 3 cases. He says the treatment depends on the condition which is present. In cases in which there is a bony union, operation must be performed. If the muscles only are affected, gymnastic methods are indicated.

*Fusion of the Lumbar Portion of the Spine.*—Hadley<sup>133</sup> also reports a case of fusion of the third and fourth lumbar vertebrae. He reviews the literature and from it describes the formation of these deformities. He says:

In the embryo the first anlage of the spine is a longitudinal column of ectodermal cells called the notochord, which forms beneath the neural groove. Paralleling this notochord are longitudinal groups of mesodermal cells and paraxial mesoblasts. These two paraxial masses undergo segmentations, producing 37 somites. These somites become sclerotomes which grow toward each other around the notochord. The sclerotomes divide into two parts, the less dense cranial portion becoming the anlage of the intervertebral disc and the more dense caudal portion of the scleromere or primitive vertebral body. The scleromeres become transformed into dense cartilage, there being at first two centers of chondrification.

He presents roentgenograms showing fusion of the third and fourth lumbar vertebrae.

*Deformities of the Extremities.*—Levy<sup>134</sup> reports the case of a still-born female infant of Greek descent who showed a complete absence of all four extremities. The head and the trunk were normal in appearance.

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132. Hadley, H. G.: Sprengel's Deformity, *Radiology* **36**:624-626 (May) 1941.

133. Hadley, H. G.: Case of Fusion of Third and Fourth Lumbar Vertebrae, *Radiology* **36**:108 (Jan.) 1941.

134. Levy, J. L.: Girl Born Without Legs and Without Arms, *South. M. J.* **34**:1085 (Oct.) 1941.

Von Hagen<sup>135</sup> reports malformations of both the upper and the lower limbs in a Negro child. There was 1 half brother with similar deformities, also 2 half brothers with inversion of the feet and 1 maternal aunt with inversion of the right foot. The right hand showed a long tapering thumb and a finger from a spur on the ulna. The left hand showed a similar thumb and two rudimentary fingers. The legs were both short, and the patient walked on his hands. There was absence of the fibula on each side with only two toes on each rudimentary foot. The author says that this case is unique in that it illustrates the transmission of deformities of the limbs probably through the germ plasm of the mother.

Meyer and Cummins<sup>136</sup> report the case of an infant with congenital constriction of the right arm with wrist drop, amputation and constriction of some of the fingers of the other hand and amputation and syndactylia of the stumps of the toes on one foot. The infant's mother had a severe accident near the end of the first trimester of pregnancy. The question is raised whether this had anything to do with the amputations and constrictions, since the mother had multiple fractures of the extremities and pelvis with osteomyelitis and several roentgen examinations of the pelvis. The authors conclude that the accident had little influence because the onset of an amputative pathologic lesion occurs at a considerably earlier period and children with amputations and constrictions are born to mothers who have had no severe trauma.

*Deformities of Hands and Feet.*—Johnson<sup>137</sup> reports a case of a 72 year old patient who had congenital amputation of some fingers, partial syndactylia with congenital constrictions of some of the fingers and a constricting band about the right lower leg. The case is reported from a dermatologic clinic. Johnson says:

This congenital anomaly is a rarity in medical practice since similar cases in an embryological laboratory which received many of the monstrosities and curiosities of medicine are conspicuous by their absence.

This man had edema above and below the constriction on the leg after no trouble for seventy years. [ED. NOTE: This is a fairly common deformity of the fingers and of the lower leg and is seen from time to time in any orthopedic clinic.]

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135. von Hagen, K. O.: Congenital Malformations of Upper and Lower Extremities in Siblings with Different Fathers, Bull. Los Angeles Neurol. Soc. 6:82-84 (June) 1941.

136. Meyer, H., and Cummins, H.: Severe Maternal Trauma in Early Pregnancy: Congenital Amputations in Infant at Term, Am. J. Obst. & Gynec. 42: 150-153 (July) 1941.

137. Johnson, H. M.: Congenital Cicatrizing Bands: Report of Case with Etiologic Observations, Am. J. Surg. 52:498-501 (June) 1941.



Inman,<sup>138</sup> in an article on the embryology of hereditary brachydactyilia in a rabbit, says:

The shortening or absence of some portion of the limb occurs as a hereditary character in man, mouse, fowl, and rabbit. Developmental study of such a character at the time when it is being established is of interest insofar as it gives an indication of the processes by which a gene acts to produce its effects. . . . [The character] is of importance from physiological and embryological viewpoints, because the abnormal development may prove to be due to metabolic disturbance or to defective tissues.

Studies of human embryos show that fluid collects within the epidermis, although it is sometimes found lying below the epidermis. In many cases the abnormality is so far advanced that the original nature of the defect cannot be determined.

Careful histologic study was made of rabbit embryos from the twelfth to the twenty-first day of gestation. .

. . . On the twelfth day a destructive process may already have begun, for the endothelial cells of the limb vessels are swollen. Following this very early stage, vessels of the limb bud . . . become dilated and, either through rupture or degeneration, lose their thin endothelial wall. This permits the escape of fluid and blood cells, and the fluid penetrates into the mesenchyme, separating the cells. Necrosis of the edematous tissue follows. There is continued bleeding into the affected area, and other smaller foci may be established. The process reaches its height, apparently, during the sixteenth to eighteenth days. There follow typical reparative processes: Necrotic material is removed by phagocytosis and fibrous tissue fills in the defect. Areas of irreparable injury are sloughed off, following their sequestration by down-growth of epithelium.

Cohn and Ravin<sup>139</sup> report an unusual case of brachydactyilia. They state that the manifestations of brachydactyilia are legion. The patient whose case they present had bilateral, symmetric, brachydactylous index valgus and hallux valgus. The roentgenograms reveal that the condition was not simple brachydactyilia; the triangular bones are apparently extra bones resulting from abnormal segmentation of the digital mesoblastic tissue. This interpretation receives some confirmation from the observation that the valgus deformities were evident at birth; the brachydactyilia, on the other hand, became manifest with age, as is usual in cases of simple brachydactyilia. It has been shown that brachydactyilia is usually transmitted as a dominant characteristic. The deformities in this case, however, were apparently recessive.

Austin<sup>140</sup> in reporting a case of macrodactyilia says:

Macrodactyly consists of a congenital overgrowth of one or more fingers or toes. The structures are said to be "normal in character and merely gigantic in

138. Inman, O. R.: Embryology of Hereditary Brachydactyly in Rabbit, *Anat. Rec.* **79**:483-505 (April 25) 1941.

139. Cohn, B. N. E., and Ravin, A.: Unusual Case of Brachydactyly, *J. Heredity* **32**:45-48 (Jan.) 1941.

140. Austin, W. E.: Cast of Macrodactyly, *Canad. M. A. J.* **45**:158 (Aug.) 1941.

size for the age of the individual (Rose and Carless)." The condition may be combined with syndactyly. The phalanges are enlarged as well as the soft tissues, though the hypertrophy of the latter is proportionately greater. The condition is of more than academic interest only when the affected member is sufficiently large to be troublesome. The treatment is then amputation or disarticulation.

In his case the patient was an American Indian girl who had enlarged second and third toes. These were disarticulated at the metatarsophalangeal joints; after this she was able to wear shoes of the same size.

Brinitzer<sup>141</sup> reports an unusual case in which the patient was a 60 year old man from Bangalore, India, with enlargement of the thumb and the index finger of the right hand:

As long as he [the patient] can remember he has had the deformity. At first this consisted of only a slight thickening and lengthening of the right thumb and forefinger, but throughout his life it has continued to grow. At 25 his hand was about half its present size. At 45 the middle finger started growing. Until he was 50 he could eat with his right hand. . . . The circumference of the right forefinger ( $9\frac{1}{2}$  inches) is the same as that of the left (healthy) upper arm. The length (13 inches) is 2 inches more than the left forearm. The circumference of his right thumb is . . . more than that of the normal left wrist. . . . The right forearm shows a subcutaneous lipoma. . . . Exostoses are seen [by roentgen examination] in connection with the upper end of the radius.

The author states that the relations between tumors and malformations are intimate and that it is hard to draw a dividing line between them. He defines a tumor

. . . as a mass of tissues growing without any regard to the laws which govern and restrain the growth of normal tissue. Gigantism, partial or universal, falls in the same group. . . . Is the existence of three different kinds of tumors on the same extremity [tumor, exostosis and lipoma] a mere coincidence?

Sachs<sup>142</sup> reports on 32 patients in five generations who had a short middle phalanx of the fifth finger. In some of these cases the condition caused the finger to be angulated. In all of the cases it was noticed at birth. The author discusses the various theories and states that until a better explanation is offered he is forced to conclude that brachyphalangia is due to heredity and is a familial characteristic.

Under the heading of curiosities Mouchet<sup>143</sup> presents the roentgenograms of a 7 year old girl who showed multiple congenital deformities of the ring and middle fingers of the right hand. There were three extra fragments of bone between these two fingers, and the fingers were incomplete.

141. Brinitzer, W.: Dactylomegaly; Case Note, *Indian M. Gaz.* **76**:286-287, 1941.

142. Sachs, M. D.: Familiar Brachyphalangy, *Radiology* **35**:622-626 (Nov.) 1940.

143. Mouchet, A.: Osseous Puzzle as Revealed by Roentgen Study of Syndactyly of Middle and Ring Fingers, *Presse méd.* **48**:917 (Nov. 19) 1941.

McGavack and Reinstein<sup>144</sup> report the case of a patient with congenital deformities and mental retardation. In their summary they state:

A female patient is described in whom multiple hereditary skeletal deformities are associated with mental deficiency, microcephaly, internal frontal hyperostosis and endogenous obesity.

The bony changes include brachydactyly, hyperphalangism, and brachymetapodism of the hands; and brachydactyly, and hypophalangism of the feet.

A survey of three generations of the family reveals the presence of similar disturbances in the hands of a sister and a niece.

The deformities in this case and those already found in the literature are compared.

Growth arrest at a particular time in somatic development is emphasized as the underlying hereditary trait in this and similar conditions.

*Bipartite Patella.*—Tabb and associates,<sup>145</sup> writing on bipartite patella, say that the recognition of this condition is of importance from both the medicolegal and the economic viewpoint. Bipartite patella is a term applied to an anomaly of the patella which is not commonly found but which, when discovered, is often confused with fracture.

. . . The condition was first described, according to Neviaser, in 1883. Its antiquity was demonstrated in 1902 by Kempson, who found evidence of it in an Egyptian mummy, and the first X-ray demonstration of the anomaly was made as early as 1903. Attention was again called to it during the World War when many soldiers were found to have the anomaly. Since that time occasional articles and case reports have appeared . . .

The patella develops from one or more centers. It appears about the third year, and ossification is complete at puberty. A number of writers associate the condition with osteochondritis, especially of the tibial tuberosity. In soldiers trouble came on after forced marches, and some were thought to be malingering.

There is less tenderness than in fracture, less swelling and no bloody fluid in the knee. Active extension is present.

They report 5 cases; in 4 of these the condition was bilateral. The importance of making roentgenograms of the opposite knee is stressed.

*Absence of the Fibula.*—Scott,<sup>146</sup> reports a case of congenital absence of the fibula in a premature infant. He summarizes by saying:

In addition to absence of the fibula this syndrome characteristically consists of: (1) shortening, anterior bowing and dwarfing of the affected leg; (2) shortening and anterior bowing of the tibia; (3) equinovalgus position of the foot, with

144. McGavack, T. H., and Reinstein, H.: Brachydactyly, Polyphalangism and Brachymetapodism in Moronic Individual with Microcephaly, Internal, Frontal Hyperostosis and Endogenous Obesity, *Am. J. Roentgenol.* **45**:55-62 (Jan.) 1941.

145. Tabb, J. L.; Faulkner, D. M., and Smith, C. D.: Bipartite Patella, *Virginia M. Monthly* **67**:475-478 (Aug.) 1940.

146. Scott, R. B.: Congenital Absence of Fibula: Its Occurrence in Premature Negro Infant, *Am. J. Dis. Child.* **61**:1037-1043 (May) 1941.

relaxation of the ankle joint; (4) absence of the external malleolus; (5) absence, delay in appearance or fusion of some tarsal and metatarsal centers of ossification, and (6) absence, webbing or hypoplasia of the toes.

The deformity apparently results from an intrinsic defect in the germ plasm.

The prognosis for good function generally is not very satisfactory. The diagnosis should be made in the newborn period and an orthopedist consulted about the patient's management before atrophy of disuse appears.

In discussing orthopedic treatment he states:

Ordinarily, immobilization by a cast and the wearing of corrective shoes are given an initial trial in an effort to aline the foot with the tibia. If this preliminary treatment fails, Harmon has recommended operative lengthening of the posterior and lateral tendons, followed by immobilization in a cast and the use of braces. Constant and early weight bearing is further advised to act as a stimulus to longitudinal growth. Later, the shortening due to the bend in the tibia . . . may be so great that amputation will be necessary.

*Clubfoot.*—Sell<sup>147</sup> reviews a series of 62 patients with congenital clubfoot treated by the multiple cast method. In 17 per cent of his cases there was enough inward torsion of the tibia to need correction. The amount of inward torsion is determined after the equinovarus deformity has been corrected. In a case in which inward torsion is present, he says that

. . . when the child is walking, the weight-bearing thrust falls obliquely across the long axis of the foot and drives the scaphoid around to the medial side of the head of the talus with re-creation of the adduction deformity of the forefoot. If this same vicious force is allowed to continue, varus of the heel and inversion of the foot will follow the adduction deformity. These undesirable sequelae to correction of clubfoot can be obviated if a rotation osteotomy of the tibia is done when tibial torsion is present. . . . Tibial torsion of 15 degrees or more should be treated surgically after the equinovarus deformity has been corrected.

He prefers the controlled rotation osteotomy of O'Donoghue to the simpler transverse osteotomy.

[ED. NOTE: When one of us (J. H. K.) first began treating clubfoot, many recurrences were explained by the presence of inward torsion of the tibia, and many osteotomies were done. By a more complete correction of the original clubfoot deformity and a willingness to again treat a recurrence, an osteotomy for the correction of inward torsion has not been necessary for a number of years.]

Mau<sup>148</sup> presents a statistical study of 27,843 cases of congenital clubfoot collected from the literature. He finds a sex incidence of 66.59 per cent male patients and 33.41 per cent female patients—twice as high among male patients as among female patients. He includes a critical review of the recent work of Zimmer.

147. Sell, L. S.: Tibial Torsion Accompanying Congenital Clubfoot, *J. Bone & Joint Surg.* **23**:561-566 (July) 1941.

148. Mau, C.: Sex Ratio in Congenital Clubfoot, *Ztschr. f. Orthop.* **71**:94-106, 1940.

Støren<sup>149</sup> reports an operation which he has devised for inveterate clubfoot. Through a medial longitudinal incision he divides the medial half of the achilles tendon. The long flexor tendons of the toes, and the anterior and posterior tibial tendons are lengthened. A dorsal skin flap is pulled down for closure of the wound. A plaster bandage is applied with the foot in the corrected position. The skin defect is repaired by a Thiersch graft through a fenestra. Four weeks later the achilles tendon is lengthened through a lateral longitudinal incision, and the heel is pulled down with a Schede apparatus. Four or five weeks later a wedge osteotomy is done in front of, or in, Chopart's joint, according to roentgen findings. The author says that the results of this operation were better than those he had seen previously.

Bentzon and Thomasen<sup>150</sup> present a statistical account of all cases of clubfoot in which examination and treatment were carried out at the Orthopedic Hospital at Aarhus, Denmark, from September 1936 to May 1939. The series includes 131 patients, 72 per cent of whom were male. In 63 cases the condition was bilateral. History of familial occurrence was obtainable in 14 per cent. The authors say that hereditary clubfoot is most often bilateral. One hundred cases were available for final evaluation. All the patients were given preliminary treatment in the first year of life. Ten of these required manipulations at the age of 1 year. Eighty-nine of the remaining 90 had subsequent lengthening of the achilles tendon. Fifty per cent later showed marked relapse for which secondary manipulation or cuneiform tarsectomy was indicated. The latter was performed on 23 of these patients. The authors urge more thorough early preliminary treatment.

Harry<sup>151</sup> strongly recommends the use of Denis-Browne splints in the treatment of talipes equinovarus. He expresses the opinion that the introduction of the Denis-Browne splints should be the beginning of a new era in the treatment of clubfoot. The principles involved in the use of these splints are outlined, and the technic is described in detail. The splints consist essentially of two simple yet ingeniously devised foot pieces to which each foot is strapped separately. These are bolted to a cross bar. Children are happy in these splints and enjoy an astonishing degree of activity. The treatment is continued for seven months. Prolonged treatment diminishes the danger of relapse. After the splints are removed, the child should walk in boots with valgus wedges. [ED. NOTE: One of us (J.H.K.) has given these

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149. Støren, H.: Operative Treatment of Inveterate Clubfoot in Older Children and Adults, *Acta orthop. Scandinav.* **11**:135-137, 1940.

150. Bentzon, P. G. K., and Thomasen, E.: Treatment of Congenital Clubfoot, Especially Relapsing Cases, *Acta orthop. Scandinav.* **11**:129-134, 1940.

151. Harry, N. M.: Denis-Browne Splints in Treatment of Talipes Equinovarus, *Australian & New Zealand J. Surg.* **11**:117-122 (Oct.) 1940.

splints a trial after seeing the work of Stuart Thomson in Toronto, Canada, in June 1941. At first they seemed to be the realization of a lazy man's dream. However, with longer use, it was noted that it took as long for correction with these splints as with plaster and that with them it was not possible to hold the foot so accurately or to get such thorough correction. The forefoot adduction could not be thoroughly corrected, and in correcting the equinus the feet were brought up in too much valgus, producing flatfoot. Children seem to this editor to be more comfortable in plaster casts. Even though plaster casts cost more and require more time and skill in their application, this editor is willing to go to this extra trouble to get a better result.]

The Moreaus<sup>152</sup> made a study of the roentgenograms of talipes valgus and varus because they were not able to find any roentgenographic studies of these conditions. They describe their technic, which requires exposure of one second. Midpoints are marked on the bones and lines drawn which indicate the inclination of the bones. [ED. NOTE: One of us (J. H. K.) found that a better roentgenogram can be obtained of the foot of a struggling crying baby by increasing the kilovoltage and reducing the exposure to one quarter or one tenth of a second.]

Imhauser<sup>153</sup> describes a new instrument which has been found of value in the application of plaster casts in cases of congenital clubfoot and contracted flatfoot. One advantage is that the patient complains much less of pressure pain even in the maximal position of correction. The instrument is made of light metal and was devised to maintain the foot in the best possible corrected position in the cast after preliminary redressing. In ordinary casts there is always a tendency for the foot to work its way back into more or less faulty position. The mode of application is described in detail, and illustrations show the shape of the instrument and its use. The instrument is applied over a thin wadding before the cast is applied with one end protruding and forming a sort of handle or lever with which the position of the foot can be governed. After the cast has hardened the instrument is removed.

#### IV. CONGENITAL DISLOCATION OF THE HIP

*Causation.*—According to Storck<sup>154</sup> congenital dislocation of the hip is due to lack of space in the uterus caused by placenta praevia, retroflexio uteri, uterus arcuatus, uterus bicornis or breech position. The primary factor seems to be the last mentioned. There seems also

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152. Moreau, M. H., and Moreau, J. E.: Roentgen Study of Talipes Valgus and Talipes Varus, *Prensa méd. argent.* **28**:337-340 (Feb. 5) 1941.

153. Imhauser, G.: Instrument for Application of Corrective Cast in Congenital Clubfoot and Contracted Flatfoot, *Ztschr. f. Orthop.* **71**:265-268, 1940.

154. Storck, H.: Etiology and Early Diagnosis of Congenital Dislocation of the Hip, *Med. Klin.* **36**:342-343 (March 29) 1940.

to be a connection between breech presentation and hereditary twin births. Leun<sup>155</sup> reports the case of a mother who delivered 2 children in 1936 and 1937, respectively, in breech presentation and delivered a child with facial presentation and dislocation of the left hip in 1939. In 1940 she again delivered a child in breech presentation. Although the child with dislocation of the hip was delivered in facial presentation, it is possible that this had been preceded by breech presentation which changed during the last weeks of pregnancy. The facts that the mother herself was a twin and that twins occurred twice among her siblings support the theory of a relation between breech presentation and twin pregnancy. Further investigation is urged as to the relations between dislocation of the hip, intrauterine lack of space, breech presentation and twin pregnancy.

Müller-Alberti<sup>156</sup> states that besides the large number of constitutional congenital dislocations of the hip there is a smaller group of teratologic congenital dislocations of the hip; the former are endogenous in origin, the latter exogenous. The two types can be distinguished both clinically and roentgenologically. A case is described in which torsion of the umbilical cord about a leg was the cause of the deformity. A sister of the patient had congenital torticollis which presumably had developed prenatally owing to abnormal intrauterine conditions.

Chapple and Davidson<sup>157</sup> have studied the intrauterine positions of the fetus by determining the position of comfort of the newborn child. This position in the case of congenital deformities corresponds with a fixed position within the uterus which could explain the development of the deformity. They present illustrations of congenital dislocation of the hip, genu recurvatum, torticollis and clubfoot in proof of their theory.

Emphasis is placed on the importance of routine determination of the position of comfort in all newborn babies "as an aid in the interpretation of existing deformities and as a means of anticipation and prevention of bone and joint abnormalities."

[ED. NOTE: This is an interesting study of the mechanical causation of congenital deformities due to intrauterine conditions.]

*Pathologic Nature.*—Brundiers<sup>158</sup> writes that systematic measurement of the angle of the femoral neck in cases of congenital dislocation of the hip has shown typical coxa valga which increases to the twentieth

155. Leun, W.: Problem of Insufficient Intrauterine Space and Dislocation of Hip, *Zentralbl. f. Gynäk.* **65**:380-383 (March 1) 1941.

156. Müller-Alberti, W.: Teratologic Congenital Dislocation: Etiology and Pathogenesis, *Med. Klin.* **37**:609-611 (June 13) 1941.

157. Chapple, C. C., and Davidson, D. T.: Study of Relationship Between Fetal Position and Certain Congenital Deformities, *J. Pediat.* **18**:483-493 (April) 1941.

158. Brundiers, A.: Coxa Valga in Congenital Dislocations, *Deutsche Ztschr. f. Chir.* **254**:39-47, 1940.

year with slight differences in male and female patients. He presents proof that in the great majority of cases one has not to deal with an actual increase of the angle of the neck of the femur but with a fixation in the fetal position of coxa valga (150 to 160 degrees). [ED. NOTE: It is well known that coxa valga of 150 degrees or more is present in the fetus. At birth it may be more than 140 degrees. The degree of coxa valga becomes less during infancy and childhood. This is due to the mechanics of weight bearing and muscular action in the normal hip. The persistence of the earlier degree of coxa valga has been frequently noted in children with early infantile paralysis which has interfered with the normal mechanics of weight bearing and the muscular function of the hip. One may suspect a similar explanation of the persistence of coxa valga in dislocation of the hip.]

Severin<sup>159</sup> demonstrates the advantages of arthrography of the hip by injecting a contrast medium into the hip joint. It assists in outlining the structures of the joint and in revealing the abnormal anatomic characteristics.

*Treatment.*—(a) Prevention: Frejka<sup>160</sup> states that prevention of congenital dislocation of the hip can be accomplished only during the first half year. During this period 20 per cent of congenital pelvic dysplasias undergo spontaneous correction. In 60 per cent there occurs spontaneous healing in the subluxated position. It seems probable that the position of the hip in this 60 per cent could be influenced during the first three months by a simple abduction position. An abduction splint is sewed into the ordinary swaddling cushion and keeps the limbs in permanent abduction. Routine abduction exercises may be given.

(b) Reduction: Kopits<sup>161</sup> writes that the greatest obstacle to reduction by the Lorenz method consists in marked shortening of the adductors. In those cases in which the leg is considerably shorter and in which the trochanter accordingly is high, reduction by the Lorenz method can be accomplished practically only at the expense of rupturing the adductors or by loosening their attachments at the points of insertion. With the author's method of reduction the stretching of the adductors is not required for the reduction per se but needed only for adjustment of the limb afterward into the primary Lorenz position. The child is placed on the normal side on the operating table. An assistant fixes the pelvis by holding the symphysis with one hand and the iliac spine of the affected side with the other. The operator seizes

159. Severin, E.: Arthrograms of Hip Joints of Children, Surg., Gynec. & Obst. **72**:601-604 (March) 1941.

160. Frejka, B.: Prevention of Congenital Dislocation of Hip with Abduction Pad, Wien. med. Wchnschr. **91**:523-524 (June 21) 1941.

161. Kopits, J.: Treatment of Congenital Dislocation of the Hip by Anterior Rotation of Femur, Orvosi hetil. **85**:131-133 (March 15) 1941; Rational Therapy of Congenital Dislocation of the Hip, *ibid.* **84**:513-514 (Oct. 5) 1940.



the limb above the knee joint with his left hand so that he can feel the femoral condyles. The limb is sharply adducted and rotated inward to the required degree, while the operator places his right thenar eminence on the greater trochanter. With steady traction on the limb the trochanter is now forced downward and forward with the right hand; this enables the caput to slip easily into the acetabulum. The child is then placed on the back without relaxation of the traction. The adductors are slowly stretched, while the limb is now brought into the correct position of Lorenz. In the deeply narcotized child the stretching of the adductors can be accomplished in this way without rupture. Great force should never be used in reduction. The author has used this method for thirty years in the majority of his 2,800 cases. [ED. NOTE: This method of reduction somewhat resembles the method employed by G. G. Davis, who secured reduction by pressure of the palm of the hand on the great trochanter to force the head forward into the acetabulum while the thigh was flexed at the hip.]

(c) Results of Bloodless Reduction: Severin<sup>162</sup> has made a study of 454 hips in which primary bloodless reduction was done between the years 1913 and 1932. The end results five to twenty-seven years after reduction were as follows: (1) perfect (normal in roentgen appearance), 4.24 per cent; (2) moderate deformation of the head in the acetabulum, 7.14 per cent; (3) dysplasia, not subluxation, 8.04 per cent; (4) subluxation, 43.75 per cent; (5) head in a secondary acetabulum in the upper part of the original acetabulum, 12.95 per cent; (6) redислоcation above the primary acetabulum, 16.96 per cent; (7) not reexamined, 6.92 per cent.

Functional results were better than the anatomic results, but function became impaired with advancing years unless the anatomic structures were normal or nearly normal.

Arthrographic studies showed that the joint space enlarges gradually after reduction.

These studies support the modern view that only seldom do perfect hips develop after bloodless reduction and that the majority result in subluxation and luxation. They indicate the necessity for some surgical procedure as soon as subluxation begins to appear.

[ED. NOTE: This is a supplementary study to that reviewed in "Progress in Orthopedic Surgery for 1940,"<sup>163</sup> to which the reader should refer.]

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162. Severin, E.: Late Results of Closed Reduction of Congenital Dislocation of the Hip and Arthrographic Studies of Recent Cases, *Acta chir. Scandinav.* (supp. 63) **84**:1-142, 1941.

163. Progress in Orthopedic Surgery for 1940: A Review Prepared by an Editorial Board of the American Academy of Orthopaedic Surgeons, *Arch. Surg.* **43**:492-493 (Sept.) 1941.

Schede<sup>164</sup> reports the results of treatment of congenital dislocation of the hip during the past fifteen years at his orthopedic clinic at the University Hospital in Leipzig, Germany. He defines cure and describes the preliminary result lasting to puberty and final or end results. Treatment consists of early treatment and after-treatment. The former consists of fixation in bilateral casts, even in cases of unilateral dislocation. For after-treatment the child is placed in an open cast when resting and given a tricycle for exercise. The tricycle permits grading of strain and adjustment to desired degree of abduction. The functional restitution is followed up by roentgen therapy, and the joint is usually weight bearing one-half year after beginning of the functional treatment. The disturbances developing during puberty are described, and the indications for plastic intervention on the acetabulum are given. It is indicated in cases in which long treatment by conservative measures has been without success. The best age for operation is discussed.

(*d*) Operative Treatment: Ryerson's<sup>165</sup> innovation consists of the use of a rectangular piece of bone from the side of the ilium. He drives this into the ilium immediately above the head of the femur in such a manner that it is directed downward over the outer side of the head. [ED. NOTE: The importance of constructing the shelf so that it is an integral part of the roof of the acetabulum has for a long time been emphasized. Unfortunately, the illustrations accompanying Ryerson's article demonstrate that this has not been uniformly accomplished. A gap is left between the shelf and the roof of the acetabulum. The only novelty in this operation is the use of a piece of bone taken from the posterior portion of the side of the ilium. It is an improvement only over faulty methods of shelf construction, which are indeed too prevalent.]

Lucas<sup>166</sup> elevates a flap of bone from the side of the ilium above the original acetabulum. His method differs from the usual procedure in that the free border of the flap is below and its base above. This flap is pried outward and held in this position by a wedge of bone which is inserted between the flap and the ilium and which fills in the gap made by prying the flap outward. A solid wide ledge or buttress of bone is thus constructed above the acetabulum. The head of the femur still covered with capsule is then placed beneath this buttress. The author reports 9 cases in which the result of this operation was

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164. Schede, F.: Results of Author's Therapy of Congenital Dislocations of the Hip, *Ztschr. f. Orthop.* **71**:3-67, 1940.

165. Ryerson, E. W.: Improved Shelf Operation at Hip, *J. Bone & Joint Surg.* **23**:782-787 (Oct.) 1941.

166. Lucas, L. S.: Shelf Operation for Congenital Dislocation of Hip: New Technique for Old Irreducible Dislocation, *J. Bone & Joint Surg.* **23**:819-829 (Oct.) 1941.

satisfactory. The illustrations support his statement. [ED. NOTE: One can see some difficulties and dangers attendant on this method of operation, but the author has apparently successfully avoided them. Many years ago one of us (A.B.G.) tried to turn a bone flap upward in a similar manner but finding it difficult to do without breaking it off at its base gave up the idea. The author properly emphasizes the advantage of the extracapsular operation. His operation seems well worthy of trial in suitable cases.]

In a study of private patients at the University of Toulouse, France, Charry<sup>167</sup> analyzes conditions favoring development of severe limping. Efficient treatment must be directed against each of three elements of the disorder: limping, pain and fatigue. Therefore he recommends the following measures: constructing a low shelf, subtrochanteric osteotomy for support, straightening osteotomy, shortening of one extremity for inequality of length and drilling of the neck of the femur in cases in which arthritis deformans is present. He uses his own technic for establishing the low shelf without section of the gluteus muscles, while for osteotomy he uses the wire method and malleable osteosynthesis plates. For shortening of the limb he also uses his own technic, a modification of Hugo Camera's method. Cosmetic results are excellent. For poor union of fractures of the femoral neck he uses the same methods as for congenital dislocation but prefers subtrochanteric osteotomy for support for better functioning of the limb.

Bonadeo Ayrolo and Anibaldi<sup>168</sup> present reports of 2 cases to illustrate the results of osteotomy of the femur in the treatment of inveterate congenital dislocation of the hip. Subtrochanteric osteotomy was devised as a palliative operation for old inveterate and posterior dislocations of the hip. The indications for these extra-articular corrective interventions are pain, fatigue and deformity. The 2 patients here described had bilateral dislocations. One patient was 16 and the other 22 years of age. One was treated with high and the other with low osteotomy. The latter gave good immediate results, and the functional results after five years were satisfactory, permitting the patient to continue his work.

The operation of high osteotomy was done on the other patient nine months before the time of writing. The pain and the fatigue disappeared completely, but the external deformity persisted, possibly influenced to some extent by the obesity of this patient.

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167. Charry, R.: Present Status of Surgery of Hip in Inveterate Insufficiency (in Congenital Luxation or Following Fracture of the Femoral Neck) with Extreme Claudication: Results of Author's Practice, *Cir. ortop. y traumatol.*, Habana 8: 37-49 (April-June) 1940.

168. Bonadeo Ayrolo, A., and Anibaldi, N.: Inveterate Congenital Luxation of the Hip, Osteotomy of Femur in Therapy: Cases, *Semana méd.* 2:1482-1484 (Dec. 26) 1940.

## V. CONDITIONS INVOLVING GROWING AND ADULT BONE

*The Thyroid Gland and the Skeletal System.*—The gross and obvious changes produced by hypothyroidism are those of the cretin dwarf. Wilkins and Fleischmann<sup>169</sup> summarize their studies, which they consider "only a beginning in the search for more specific and objective methods of measuring the function." Among 92 patients with dwarfism the condition of only 42 could be definitely attributed to a deficiency in thyroid secretion. One woman aged 20 probably had a mixed pituitary-thyroid deficiency; the thyroid inadequacy was proved by a biopsy which showed an atrophic gland. In the remaining cases, though at times there were suggestions of glandular deficiency, the condition could not be blamed on a deficient thyroid gland. Since the usual skeletal changes may be simulated by other diseases, it is desirable to note other functions, e. g. mental sluggishness, dryness of the hair, depressed cardiac output and pulse rate, grayish coloring of the face and mottling of the skin. In addition laboratory tests are of value. The basal metabolic rate is difficult to determine in these children and is only partly reliable and should not be considered a specific diagnostic procedure. On the other hand, a high cholesterol value is suggestive and the use of thyroxin produces changes that are valuable diagnostically. A single dose of 2 to 4 mg. of thyroxin will produce an appreciable drop in the serum cholesterol lasting for one or two months before return to the original level, whereas in the normal child only a slight transient change will be noted.

Epiphysial dysgenesis, Wilkins<sup>170</sup> states, is also characteristic of hypothyroidism. In this condition the developing epiphysial caps do not develop from a single focus but show multiple irregular foci, i. e. a picture of stippling or fragmentation. Under thyroid therapy these areas enlarge and coalesce to produce a normal-looking epiphysis.

The specificity of thyroid action on cretins is revealed by Beard,<sup>171</sup> who treated a 16 year old patient with anterior pituitary extract and found no change in any of the usual functions, while desiccated thyroid produced prompt improvement in the clinical and laboratory observations. No additional benefit could be observed when pituitary extract and thyroid gland extract were used together.

Wilkins and Fleischmann,<sup>169</sup> using the thyrotropic hormone of the pituitary gland, found that the cretin did not show the normal changes in creatine and serum cholesterol.

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169. Wilkins, L., and Fleischmann, W.: Diagnosis of Hypothyroidism in Childhood, J. A. M. A. **116**:2459-2465 (May 31) 1941.

170. Wilkins, L.: Epiphysial Dysgenesis Associated with Hypothyroidism, Am. J. Dis. Child. **61**:13-34 (Jan.) 1941.

171. Beard, E. E.: Cretinism: Lack of Response to Anterior Pituitary Growth Principle, J. Clin. Endocrinol. **1**:293-296 (April) 1941.

The effects of hyperthyroidism on the skeleton are again brought to attention by Mansbacher.<sup>172</sup> He reports the cases of 2 patients, women near 60, who had had hyperthyroidism for a long time and who showed generalized decalcification. The causative relationship is demonstrable by the artificial stimulation of the metabolism by desiccated thyroid, after which the increased calcium excretion is appreciably lower in the patient with myxedema than in the normal person. The author suggests that in all patients with thyrotoxicosis pain in the spine or the extremities be studied for porosis and expresses the opinion that the administration of a high calcium and vitamin diet should be helpful. In Brunner's<sup>173</sup> report on 22 patients with hyperthyroidism there were 10 cases of malacia. In the 2 worst cases the patients were women. He too feels that it is right to attribute the decalcification to the hyperthyroidism.

*Parathyroid Glands and Bony Changes.*—The importance of the parathyroids in the control of bone structure and density has been fairly well established in recent years. The correlation of the changes in these two structures is still being reported in the literature, but the simplicity of the causal relationship is being challenged. More and more the kidney is to be found entering the picture. Leverton<sup>174</sup> presents a fairly concise description of the role of the parathyroid hormone in calcium metabolism. Brunner<sup>175</sup> reports a case of osteitis fibrosa cystica in which hyperparathyroidism and calcium diabetes were cleared up by parathyroidectomy. Gentile, Skinner and Ashburn<sup>176</sup> have collected a number of described cases of parathyroid tumors and add 1 of their own of malignant lesion of this gland. Their patient showed marked decalcification with fractures. Removal of the gland was followed by healing of the fractures and recalcification of the bones. Wise<sup>177</sup> and Chapman<sup>178</sup> each report a case in which the patient had adenoma of the parathyroids with giant cell tumor changes. Wise noticed a restoration of the skeletal system and the blood calcium following removal of the tumor.

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172. Mansbacher, K.: Osteoporosis in Hyperthyroidism, *Internat. Clin.* **3**:221-224 (Sept.) 1941.

173. Brunner, W.: Osteoporosis and Calcium Metabolism in Hyperthyroidism, *Deutsche Ztschr. f. Chir.* **254**:133-149, 1940.

174. Leverton, W. R.: Parathormone and Vitamin D: Calcium and Phosphorus Metabolism, *M. Bull. Vet. Admin.* **17**:266-273 (Jan.) 1941.

175. Brunner, W.: Calcium Diabetes (Recklinghausen's Osteitis) as Classic Form of Hyperparathyroidism: Case with Recovery After Extirpation of Parathyroid Adenoma, *Arch. f. klin. Chir.* **199**:429-438, 1940.

176. Gentile, R. J.; Skinner, H. L., and Ashburn, L. L.: Parathyroid Glands: Malignant Tumor with Osteitis Fibrosa Cystica, *Surgery* **10**:793-810 (Nov.) 1941.

177. Wise, I. M.: Osteitis Fibrosa Cystica, *South. Surgeon* **10**:819-824 (Nov.) 1941.

178. Chapman, H. S.: Hyperparathyroidism, *West. J. Surg.* **49**:386-397 (July) 1941.

In this case, however, it is noted that renal calculi appeared. Siris<sup>179</sup> also found renal calculi in his patient with osteitis fibrosa cystica. Jelke,<sup>180</sup> basing his extensive article on his studies of a woman with osteitis fibrosa cystica with parathyroid adenoma, finds many changes to indicate renal damage. Removal of the tumor resulted not only in an improved skeleton but was also followed by marked improvement of the kidney involvement.

Ginzler and Jaffe<sup>181</sup> report finding consistent changes in the skeletal system, such as fibroporotic resorption accompanied by new bone formation in a patient with chronic renal insufficiency. In cases of this sort the parathyroids show hyperplasia, but this change is believed to be secondary. The primary factor is the chronic acidosis of renal insufficiency.

Eger,<sup>182</sup> in one of a series of studies, establishes the effect of kidney changes by the experimental route. Renal damage was produced by uranium nitrate. In a few weeks bone changes of the osteitis fibrosa cystica type appeared. In some of the animals hypertrophy of the parathyroids appeared. Eger feels that the bone changes were the direct result of the acidosis.

Albright, Burnett, Cope and Parson<sup>183</sup> present a case in which the skeletal porosis was fitted into the multiple skeletal changes in a different pattern. Their patient had a solitary bone cyst which led to a fracture. Therapeutic immobilization led to osteoporosis of disuse, which resulted in hypercalcemia with kidney damage. In their case at operation there was no parathyroid hypertrophy; for this reason they express the opinion that the increased blood calcium should not per se be considered evidence of parathyroid hyperfunction. They reemphasize the fact that mobilization of the bone salts can be the result of the reduced osteoblastic activity that ensues when normal stress and strain are removed.

In the matter of therapy Rubenfeld<sup>184</sup> calls attention to the value of roentgen therapy of the glands in the cure of osteitis fibrosa cystica.

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179. Siris, I. E.: Hyperparathyroidism: Report of Case of Osteitis Fibrosa Cystica, with Pathologic Fracture and Renal Calculi Cured by Removal of Parathyroid Adenoma, *New York State J. Med.* **40**:1788-1795 (Dec. 15) 1940.

180. Jelke, H.: Hyperparathyroidism, with Special Reference to Role in Etiology of Generalized Osteitis: Case with Severe Renal Changes, *Acta med. Scandinav.*, 1940, supp. 114, pp. 1-67.

181. Ginzler, A. M., and Jaffe, H. L.: Osseous Findings in Chronic Renal Insufficiency in Adults, *Am. J. Path.* **17**:293-302 (May) 1941.

182. Eger, W.: Further Studies on Experimental Osteitis Fibrosa, *Virchows Arch. f. path. Anat.* **306**:183-192, 1940.

183. Albright, F.; Burnett, C. H.; Cope, O., and Parson, W.: Acute Atrophy of Bone (Osteoporosis) Simulating Hyperparathyroidism, *J. Clin. Endocrinol.* **1**:711-716 (Sept.) 1941.

184. Rubenfeld, S.: Hyperparathyroidism: Its Treatment with Roentgen Irradiation, *Am. J. Roentgenol.* **46**:224-231 (Aug.) 1941.

In his case surgical exposure for the parathyroids failed to show the glands; roentgen therapy was therefore resorted to. Although the chemical changes were not remarkable, symptomatic relief was obtained in conjunction with evidence of bone cyst repair.

From the point of view of roentgen diagnosis Schatzki<sup>185</sup> offers a differentiation between the film appearances of osteitis fibrosa cystica of parathyroid origin and osteodystrophic fibrosa (Albright). In the first condition the cystic areas are usually sharply punched out and frequently associated with generalized osteoporosis. The second condition, however, is unilateral, is found in otherwise healthy-looking bone and is characterized by fuzzy edges. Couch and Robertson<sup>186</sup> call attention to the fact that pagetoid changes can be noted in the roentgenograms of patients with hyperparathyroidism. They express the belief that this is due to exacerbations and remissions in the activity of the glands.

The importance of not blaming the parathyroids for all fibrocystic diseases is stressed by Thomas and associates<sup>187</sup> and Neller.<sup>188</sup> In their cases the absence of calcium and phosphorus changes in the blood and the associated skin changes led them to believe that multiple embryonic defects were responsible.

*The Pituitary Gland and the Skeletal System.*—It has long been known that the pituitary gland affects the growth of the skeletal system. Gigantism and acromegaly have been attributed to this. It has even been believed that the calcium and phosphorus content of the bones is affected indirectly by this gland. But the theory has been that alkaline pituitary extract causes hypertrophy of the parathyroids, which in turn causes hypercalcemia that results in a body loss of calcium. Bauer and Aub<sup>189</sup> however, differ with this concept. In a study of 5 cases of uncomplicated acromegaly they found that 4 patients showed an increase of calcium loss through the urine almost double the amount in normal persons. In their cases, however, there was no increase in the blood or fecal calcium, thus differentiating the condition from hyperparathyroid

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185. Schatzki, R.: Medical Progress: Diagnostic Roentgenology, Myelography, Air Versus Iodized Oil, Fibrocystic Disease of Bone, New England J. Med. **224**: 1101-1107 (June 26) 1941.

186. Couch, J. H., and Robertson, H. F.: Occurrence of Postoperative Acidosis and Pagetoid Bone Changes in Hyperparathyroidism (Due to Adenoma), Surg., Gynec. & Obst. **73**:165-174 (Aug.) 1941.

187. Thomas, H. W.; Meredith, T. N., and Wunderly, H. L.: Osteodystrophia Disseminata: Report of a Case, J. Pediat. **18**:638-642 (May) 1941.

188. Neller, J. L.: Osteitis Fibrosa Cystica (Albright), Am. J. Dis. Child. **61**: 590-605 (March) 1941.

189. Bauer, W., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: Influence of Pituitary Glands, J. Clin. Investigation **20**:295-301 (May) 1941.

decalcification. In 2 of the patients roentgen therapy to the hypophysis improved the acromegalic state and also brought about a normal urinary excretion of calcium. They state the opinion, therefore, that the calcium metabolism is directly affected by the pituitary gland.

The association of acromegaly with hyperthyroidism was the subject of a study by Davis.<sup>190</sup> In 166 cases of acromegaly the thyroid was enlarged in 50 per cent of the cases. The basal metabolic rate was correspondingly high. Removal of the thyroids of patients with acromegaly was found to be surgically risky. Furthermore, removal of the thyroid of these patients did not produce as marked a reduction in the basal metabolic rate as in normal persons. An interesting complication of acromegaly is reported by Woltman.<sup>191</sup> Two patients with this disease, complained of paresthesia and later showed trophic changes in the hands that led to the diagnosis of median nerve neuritis. In 1 patient section of the annular ligament at the wrist gave complete relief; for this reason the author expresses the opinion that the neuritic changes were of mechanical origin.

*Osteomalacia.*—Further studies on osteomalacia include the role of pregnancy in its production. Liu and associates,<sup>192</sup> studying 10 patients, show that when adequate vitamin D and calcium are fed to these patients no osteomalacia will develop. They state that the bone softening is brought about by the increased fetal need for lime salts and not by an endocrine disturbance. Albright and associates<sup>193</sup> discuss postmenopausal osteoporosis and state that it is a disease of deficient osteoblastic activity rather than a disease of calcium metabolism. Disuse and senility rather than diet are responsible factors. The postmenopausal state is the most important causative requirement.

*Osteosclerosis.*—Generalized sclerosis of the bones has been recognized and reported as a clinical picture for many years. No satisfactory explanation of the causation has been offered. It is, however, likely that the hardening of the bone is a clinical manifestation or an end result in a number of conditions. Thus it is known that fluorine poisoning can produce osteosclerosis. Pandit and associates<sup>194</sup> find

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190. Davis, A. C.: Thyroid Gland in Acromegaly: Study of One Hundred and Sixty-Six Cases, *Tr. Am. A. Study Goiter*, 1940, pp. 312-321.

191. Woltman, H. W.: Neuritis Associated with Acromegaly, *Arch. Neurol. & Psychiat.* **45**:680-682 (April) 1941.

192. Liu, S. H., and others: Calcium and Phosphorus Metabolism in Osteomalacia, Pathogenetic Role of Pregnancy and Relative Importance of Calcium and Vitamin D Supply, *J. Clin. Investigation* **20**:255-271 (May) 1941.

193. Albright, F.; Smith, P. H., and Richardson, A. M.: Postmenopausal Osteoporosis: Its Clinical Features, *J. A. M. A.* **116**:2465-2474 (May 31) 1941.

194. Pandit, C. G.; Raghavachari, T. N. S.; Rao, D. S., and Krishnamurti, V.: Endemic Fluorosis in South India: Study of Factors Involved in Production of Mottled Enamel in Children and Severe Bone Manifestations in Adults, *Indian J. M. Research* **28**:533-558 (Oct.) 1940.



that in communities with a fluoride content of drinking water of one part per million or over all children show the bony changes in conjunction with mottling of the teeth. Adults who have been subjected to this water for over fifteen years have likewise shown this manifestation of fluorine poisoning. Poor dietary control, especially lack of vitamin C, seems to be an adjunct of this intoxication. The importance of this lack of vitamin was proved by experiments on monkeys.<sup>195</sup> Fluorine intoxication was much more pronounced in animals from whose diet vitamin C was excluded.

In this country Hodges and associates<sup>196</sup> demonstrated that unless sodium fluoride is present in the drinking water in more than three parts per million no osteosclerotic changes will ensue.

Concerning the association of osteosclerosis with changes in the hemopoietic system, Horwitz<sup>197</sup> reports a case in which this manifestation, although asymptomatic, was found in a monomelic medullary distribution. The sclerotic changes were slowly progressive and diffuse, showing a compact apposition of irregular fragments of immature and mature bone with an irregular structure. All parts of the bone except the periosteum were affected. Laboratory tests gave negative results. The author postulates that this condition is of congenital origin but admits that the causation is to be proved.

Carpenter and Flory<sup>198</sup> report a case of generalized diffuse osteosclerosis associated with generalized fibrosis of the bone marrow with an erythromyelomegakaryocytic blood picture. There is splenomegaly with myeloid metaplasia. They state that this is the result of progressive hyperplasia of the mesenchymal tissues produced by an unknown stimulus.

Kramer<sup>199</sup> reports the cases of 2 brothers with marble bones, and although he calls attention to the increase in myelocytes, he stresses the concurrent anemia. Baker and Jones<sup>200</sup> also found this syndrome

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195. Pandit, C. G., and Narayana Rao, D.: Endemic Fluorosis in South India: Experimental Production of Chronic Fluorine Intoxication in Monkeys (*Macaca Radiata*), *Indian J. M. Research* **28**:559-574 (Oct.) 1940.

196. Hodges, P. C.; Fareed, O. J.; Ruggy, G., and Chudnoff, J. S.: Skeletal Sclerosis in Chronic Sodium Fluoride Poisoning, *J. A. M. A.* **117**:1938 (Dec. 6) 1941.

197. Horwitz, T.: Monomelic Medullary Osteosclerosis of Unknown Etiology, *Radiology* **36**:343-351 (March) 1941.

198. Carpenter, G., and Flory, C. M.: Chronic Nonleukemic Myelosis: Report of Case with Megakaryocytic Myeloid Splenomegaly, Leukoerythroblastic Anemia, Generalized Osteosclerosis and Myelofibrosis, *Arch. Int. Med.* **67**:489-508 (March) 1941.

199. Kramer, H.: Albers-Schönberg Marble Bone Disease, *München. med. Wchnschr.* **88**:132-133 (Jan. 31) 1941.

200. Baker, L. D., and Jones, H. A.: Osteopathia Condensans Disseminata, Osteopoikilosis (Spotted Bones): Report of Case, *J. Bone & Joint Surg.* **23**: 164-169 (Jan.) 1941.

in 2 members of a family, a 14 year old boy and his sister. In their cases there was spotted bony condensation (osteopoikilosis).

*Fragilitas Ossium.*—Riesenman and Yater<sup>201</sup> investigating 255 members of seven family groups found 91 who showed familial bone fragility. The characteristic associated changes of blue scleras and otosclerosis were noted. The authors stress the importance of orthopedic care and, since there is a marked decrease in the number of fractures at the onset of puberty, suggest the prenatal and postnatal use of thymus extract. In Bornebusch's<sup>202</sup> article much the same observations are made, although the author points out that the diaphysis is frequently the point of fracture, particularly in the lower extremities. Loesche<sup>203</sup> adds the observation that pregnancy has a deleterious effect on the osteogenetic defect, so that he considers an induced abortion with sterilization may be indicated.

*Rickets.*—The responsibility of rickets for bow leg deformities is challenged by Blount.<sup>204</sup> He calls attention to a form of bowing at the upper tibial epiphysis which he assumes to be the result of an osteochondrosis similar to that seen in coxa plana. [ED. NOTE: He does not substantiate his impression by offering reports on the microscopic appearance of the cartilage.]

The treatment of rickets is accorded a considerable amount of attention. Wagner and Jones<sup>205</sup> find that in cases of impaired gastrointestinal absorption of cod liver oil, the vitamin D can be given by skin administration. The amount used must be greater than that used orally. No skin irritation is reported to ensue. Effective therapeutics is obtained in two weeks after onset of such treatment.

Turk,<sup>206</sup> in a series of articles, proves again that oral administration of vitamin D<sub>2</sub> is reliable in a fairly large series (30 cases). Vitamins D<sub>2</sub> and D<sub>3</sub> can also be used effectively intramuscularly. Bohm<sup>207</sup>

201. Riesenman, F. R., and Yater, W. M.: Osteogenesis Imperfecta: Its Incidence and Manifestations in Seven Families, *Arch. Int. Med.* **67**:950-967 (May) 1941.

202. Bornebusch, K.: Heredity and Typical Triple Syndrome of Osteogenesis Imperfecta Tarda, *Deutsche Ztschr. f. Chir.* **254**:115-132, 1940.

203. Loesche, H. J.: Eugenic Significance of Osteogenesis Imperfecta, *München. med. Wchnschr.* **88**:162-164 (Feb. 7) 1941.

204. Blount, W. P.: Bow Leg, *Wisconsin M. J.* **40**:484-487 (June) 1941.

205. Wagner, E. A., and Jones, D. V.: Observations on Application of Vitamin D to Skin, *Ohio State M. J.* **37**:249-254 (March) 1941.

206. Turk, E.: Intramuscular Administration of Massive Doses of Vitamin D<sub>2</sub> and D<sub>3</sub> in Rickets, *Arch. f. Kinderh.* **121**:46-52, 1940; Oral Administration of Massive Doses of Vitamin D<sub>2</sub> in Rickets, *ibid.* **121**:33-46, 1940; Roentgen Study of Bones Following Massive Doses of Vitamin D<sub>2</sub>, *Med. Klin.* **36**:976-978 (Aug. 30) 1940; Massive Doses of Vitamin D in Rickets, *ibid.* **36**:862-864 (Aug. 2) 1940.

207. Bohm, K.: Intramuscular Massive Doses of Vitamin D<sub>2</sub> and D<sub>3</sub> in Children with Rickets, *Arch. f. Kinderh.* **121**:1-10, 1940.

injected 15 mg. of vitamin D<sub>2</sub> intramuscularly in 5 rachitic infants and obtained full recovery. Vitamin D<sub>3</sub> similarly used gave a full, rapid recovery, too.

The mechanism of the therapeutic effect of vitamin D is studied by Harrison and Harrison.<sup>208</sup> They believe that the rachitic state results from faulty absorption of calcium from the intestinal tract. This produces hypocalcemia which stimulates the parathyroids to overactivity, so that a low serum phosphorus is secondarily produced. The vitamin D, exerting a direct effect on the renal tubular cells, causes reabsorption of the phosphate.

The effect on the serum acid phosphatase after the injection of vitamin D<sub>3</sub> is reported by van Creveld and Mastenbroek.<sup>209</sup> In active rickets there is a high serum phosphatase, while in healed rickets it is of a normal level. Vitamin D<sub>3</sub> injected in single massive doses gave quick healing. Mouriquand and associates,<sup>210</sup> working with experimental rickets find that the roentgen evaluation is not the truest test for rachitic activity. The chemical test is most reliable.

Dwarfism as a result of rickets is receiving analytic study. Boyd and Stearns<sup>211</sup> report 3 patients with late rickets, 2½ years, 7 years and 8 years of age. In each the disease began in infancy and was attended by marked retardation of growth, hypophosphatemia not responsive to vitamin D, osteoporosis, ricket-like epiphyses and under-nutrition. In their 2 youngest patients there was also glycosuria, while in the third one there were noted polyuria and polydipsia without glycosuria.

That dwarfism of rickets is really a condition of underdevelopment associated with calcium and phosphorus metabolic disturbances with abnormal effects on the kidneys and the endocrine glands is brought out by a number of authors. Gittleman and Pincus<sup>212</sup> state that the course of events is probably as follows: A primary dysfunction of the anterior pituitary results in hyperketonuria and hepatomegaly. There ensues

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208. Harrison, H. E., and Harrison, H. C.: Renal Excretion of Inorganic Phosphate in Relation to Action of Vitamin D and Parathyroid Hormone, *J. Clin. Investigation* **20**:47-55 (Jan.) 1941.

209. van Creveld, S., and Mastenbroek, G. G. A.: Serum "Acid" Phosphatase in Rickets After Injection of One Large Dose of Vitamin D<sub>3</sub>, *Acta brev. Neerland.* **11**:5-9, 1941.

210. Mouriquand, G.; Leulier, A.; Coeur, A., and Edel, V.: Comparison of Roentgenologic Signs and Chemical Examination of Bones in Evaluation of Cure of Experimental Rickets, *Compt. rend. Soc. de biol.* **134**:144-146, 1940.

211. Boyd, J. D., and Stearns, G.: Late Rickets Resembling Fanconi Syndrome, *Am. J. Dis. Child.* **61**:1012-1022 (May) 1941.

212. Gittleman, I. F., and Pincus, J. B.: Rickets Associated with Dwarfism, Glycosuria, Ketonuria and Albuminuria, *Am. J. Dis. Child.* **60**:1351-1370 (Dec.) 1940.

acidosis with hypophosphatemia, i. e. rickets. Charnock<sup>213</sup> and Davis and Rossen<sup>214</sup> likewise state that these factors are involved, although they shuffle them about in a somewhat different sequence.

*Osteitis Deformans.*—In the domain of Paget's disease, or osteitis deformans, there are reported three complications of intraspinal involvement. Hillman<sup>215</sup> reports 1 case in which compression of the cord took place when the vertebrae expanded so as to reduce the lumen for the cord. In another patient the cord pressure resulted from fracture of the altered bone. MacKay<sup>216</sup> reported 2 cases of protruded intervertebral disk in Paget's disease.

#### VI. TUBERCULOSIS OF BONES AND JOINTS

*General Considerations.*—Rosencrantz, Piscitelli and Bost<sup>217</sup> have made a study of the orthopedic patients with tuberculosis who entered the San Francisco Hospital in the tuberculosis service of the University of California from January 1920 to July 1935.

Of 4,252 patients with tuberculosis, 160, or 3.76 per cent, had two or three tuberculous bone and joint lesions, which were usually secondary to some other tuberculous focus, most frequently in the lungs. Of these 160 patients, 73.7 per cent had chronic pulmonary tuberculosis; 26.3 per cent had no pulmonary involvement but had fifty-three bone and joint lesions, or 26 per cent of the orthopedic lesions. Of these patients with fifty-three lesions, 34 with forty-five of the lesions had manifestations of tuberculosis elsewhere, in bone and joints or the skin or as adenitis. In only 8 was one joint the sole focus of tuberculosis.

When tuberculous bone and joint lesions are associated with pulmonary disease, the outcome is greatly influenced by the degree of lung involvement and is particularly serious in the moderately advanced and far advanced stages. The care of orthopedic lesions should be secondary in importance to that of the pulmonary disease.

The prognosis is more serious in patients who have tubercle bacilli in the sputum, in patients in whom there are draining sinuses or multiple abscesses and in those with a focus of tuberculosis other than pulmonary.

213. Charnock, D. A.: Renal Rickets, *J. Urol.* **44**:850-859 (Dec.) 1940.

214. Davis, P. G., and Rossen, J. A.: Renal Rickets, *J. Pediat.* **18**:103-116 (Jan.) 1941.

215. Hillman, R. W.: Compression of Spinal Cord in Paget's Disease, *Brooklyn Hosp. J.* **3**:155-162 (July) 1941.

216. MacKay, A. R.: Association of Protruded Intervertebral Disk and Paget's Disease of Pelvic Bones: Report of Two Cases, *Proc. Staff Meet., Mayo Clin.* **16**: 138-140 (Feb. 26) 1941.

217. Rosencrantz, E.; Piscitelli, A., and Bost, F. C.: Analytical Study of Bone and Joint Lesions in Relation to Chronic Pulmonary Tuberculosis, *J. Bone & Joint Surg.* **23**:628-638 (July) 1941.

The mortality statistics in relation to treatment were as follows: Of 88 patients treated by rest or immobilization only, 49 died; the lesions of 10 were unimproved; the lesions of 15 were improved, and 14 of the patients recovered. Of 72 patients treated by operation 29 died; the lesions of 6 were unimproved; the lesions of 21 were improved, and 16 of the patients recovered. The mortality rate was greater in the cases in which there was pulmonary involvement (51 per cent) than in the cases in which there was no pulmonary involvement (38 per cent) and greatest in those in which there were multiple joint lesions.

The authors make note of the fact that the mortality rate was higher among patients of the yellow, mixed and Negro races and stress the importance of careful consideration of each patient before operation is undertaken. They emphasize also the necessity of a complete physical examination, including routine laboratory work and making roentgenograms of the chest for every patient.

Curtis and Loomis<sup>218</sup> report that tuberculosis is the most common cause of death among the people of Newfoundland and southern Labrador. In the fifteen years from 1923 to 1938, 10 per cent of the 8,778 admissions to the St. Anthony Hospital of the International Grenfell Association, St. Anthony, Newfoundland, were for tuberculosis, and 3 per cent of these were for bone tuberculosis.

This study analyzes by questionnaire and by examination when possible the results obtained in treating 157 of the 175 patients with bone tuberculosis admitted during this fifteen year period. The average follow-up period was eight and nine-tenths years. The patient's condition was considered excellent if he was able to do hard manual labor, good if he could do light work, fair if he used a crutch or other type of support and poor if he was bedridden. The patients were divided into groups: those who had no other clinical evidence of tuberculosis and those who had other tuberculous foci or a history of them in the lungs, the genitourinary tract, the peritoneum or elsewhere.

Operative treatment was employed in approximately two thirds of the cases in which the spine was involved and in one half of those in which the hip, the knee and the ankle were affected. Except for Syme amputations in 6 of the 8 cases in which the ankle was involved and in which operation was performed and for 1 amputation for extensive knee involvement, operation was done to obtain arthrodesis. Upper extremity and sacroiliac involvement were treated conservatively except for amputation for wrist involvement in 1 case.

On the basis already indicated, good results were obtained by both operative and nonoperative methods in cases of involvement of the

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218. Curtis, C. S., and Loomis, E. G.: *Bone Tuberculosis in Northern Newfoundland*, *J. Bone & Joint Surg.* **23**:811-818 (Oct.) 1941.

spine, the knee and the ankle, but a higher proportion of good results was obtained by operation in cases of involvement of the spine and the hip with no other foci of the disease. Operation, however, on the patients with other foci did not give any better results than conservative therapy.

The mortality rate for the whole series was 28.7 per cent. In the operative group the rate was 9.3 per cent for those patients who did not have other foci of the disease and 59.4 per cent for those who did. In the nonoperative group it was 17.7 per cent for those without additional foci and 50 per cent for those with them.

The authors state that from this study the futility of operating on patients with other tuberculous foci is evident. They feel that in a general hospital such as theirs conservative treatment, especially for patients with involvement of the spine and the hip, cannot be carried out because of the limited personnel trained in orthopedic nursing. They emphasize that the time of hospitalization is also a factor and point out that operative treatment with discharge from the hospital in three to six months is preferable from the viewpoint of both the patient and the hospital to conservative treatment requiring several years.

[ED. NOTE: Cleveland has emphasized the influence of an active pulmonary lesion, especially one with cavitation and with bacilli in the sputum, on the outcome of bone and joint tuberculosis and has demonstrated graphically by his statistics compiled at the Sea View Hospital in New York that the mortality rate rises markedly in such cases. The experience of the authors of the preceding articles confirms this statement. It undoubtedly is true, however, that if a joint lesion can be cured or made quiescent the patient is better able to take care of his pulmonary tuberculosis. The fact must not be lost sight of that a fairly large number of patients with active pulmonary tuberculosis complicated by a joint lesion have recurrence. All of these patients, therefore, should not be condemned, but the best judgment should be exercised in selecting those who are thought to have a fighting chance, and they should be given the benefit of surgical treatment. These unfortunate persons have everything to gain and little to lose by such a course.

The value of the study of the patients in Newfoundland is diminished somewhat by the inability of the surgeons to examine them later. A study by questionnaire is always subject to many errors. It would be helpful to know how many of the patients operated on really obtained fusion.]

*Pathologic Considerations.*—Auerbach<sup>219</sup> concludes from 119 autopsies on patients with skeletal tuberculosis that this condition is the result of a hematogenous spreading before healing of the primary focus.

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219. Auerbach, O.: Tuberculosis of Skeletal System, Quart. Bull. Sea View Hosp. 6:117-147 (Jan.) 1941.

Eighty-seven patients, or 73 per cent, had spinal involvement with multiple vertebrae involved in 82, or 94 per cent, of this number. The most frequently involved segments were those from the ninth and eleventh dorsal vertebrae. The lesion started most often near the anterior portion of the intervertebral disk. In these instances compression of the vertebral body resulted. Less commonly the bone retained its firmness, showing microscopically a productive process. In 83 of the 87 cases paravertebral abscesses were encountered. In 13 of the 87 cases there was external pachymeningitis. Joint tuberculosis occurred in 45 cases in either the wet or the dry stage. Amyloidosis was present in 35 per cent of the cases, and tuberculous meningitis was the cause of death in 13.4 per cent.

De los Santos<sup>220</sup> summarizes a pathologic study of 21 tuberculous spines as follows:

The present study is based upon 74 clinical cases of tuberculosis of the spine examined roentgenologically. Twenty-one of these cases came to necropsy and the spines [were] studied both roentgenologically and pathologically in an attempt to determine the localization, extension and healing of the tuberculous spinal infection.

The intervertebral articular type of the spinal localization has been found roentgenologically and pathologically to be the most common. The incidence is greatly increased by the rather large number of cases with posterior juxta-articular localization, which generally fails to show roentgenologically until late in the disease after marked structural changes have already taken place. The central type of localization comes next in frequency.

The tuberculous infection may find lodgement in a number of distant vertebral bodies. As high as 40 per cent of the cases pathologically studied showed multiple vertebral localization.

The spinal infection appears to follow no definite course or pattern and its extension depends to a great extent upon its initial localization. While its common course is toward the spinal canal and laterally, yet in a few instances it pursues its way along the anterior and posterior spinal ligaments with secondary involvement of the vertebrae and the intervertebral discs. Although the intervertebral discs in adults appear vulnerable to the infection, in children in most instances the discs are quite resistant to it and escape involvement in spite of destruction and even collapse of adjacent vertebral bodies.

During the extension of the infection sequestra of various sizes are commonly formed but they remain generally unrecognizable in the roentgenogram.

Fine and early sequestra are frequently made up of bone plates or ossified epiphyses following invasion by tuberculous granulation tissue. A primary epiphyseal involvement, however, has not been seen so far either from the microscopic examination or in the roentgenogram taken of a slice of the bone. The sequestra are commonly found on the anterior and posterior edges of the vertebra and are detected only upon roentgenological examination of a thin slice of the bone and upon microscopic study.

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220. De los Santos, J. V.: Tuberculosis of Spine: Observations on Localization, Extension and Healing; Their Bearing on Diagnosis and Treatment, *Bull. Quezon Inst.* 1:283-341 (Jan.) 1941.

Bilateral (kissing) sequestra are at times encountered in spite of the presence of intact intervertebral discs. Contrary to Konig's theory of embolism, their formation appears to result from secondary invasion of the bone by granulation tissue, as has also been mentioned previously by Phemister.

Aside from the common subjective and objective symptoms, roentgenological manifestations of spinal caries are important in establishing the diagnosis. The recognition is based upon the appearance of bone changes—usually in the nature of defects—in the various regions of the vertebra, which form the frequent sites of localization of the tuberculous infection; namely: intervertebral or juxta-articular, central and anterior.

The presence of abscess shadow about the lesion is an important finding but is not essential in the diagnosis. The same holds true with the angular deformity or gibbus of the spine.

Osteoperiostitis along the regions of the anterior and lateral spinal ligaments as well as new bone formation on or about the small intervertebral articulations, spinous ligaments and ligamenta flava in arrested and healing tuberculous lesions is a significant finding.

Nathanson and Cohen<sup>221</sup> report on 200 patients with bone and joint tuberculosis (100 adults and 100 children) treated at the Sea View Hospital, New York. The pediatric group included all patients up to 16 years of age; 70 per cent of these were less than 10 years old. In the adult group 77 per cent of the patients were between the ages of 16 and 45. Each case has been verified.

The spinal column was involved to a much greater extent than any other area in both groups, and next in order were the weight-bearing joints. A high incidence of small tubular bone disease was noted in the younger group. The upper dorsal portion of the spine was more frequently involved in the pediatric than in the adult group; the reverse was true of the lower dorsal vertebrae.

In contradistinction to the commonly accepted belief that bone or joint tuberculosis is monarticular, 35 per cent of the pediatric patients and 28 per cent of the adult patients showed involvement of more than one area. Forty-two per cent of the younger patients and 55 per cent of the adult patients showed some form of pulmonary tuberculous infiltration. Forty-nine per cent of the pediatric patients and 71 per cent of the adult patients had paravertebral abscess.

Marginal involvement of the vertebral body is noted more frequently in adults, and the central type of lesion is observed more often in children. Collapse of the vertebral body is a late manifestation of tuberculosis in the adult group and occurs early in the younger group. Disease in the posterior portion of the vertebral body is frequently associated with clinical evidence of cord involvement. Primary shaft disease is infrequent but not uncommon as a secondary lesion and

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221. Nathanson, L., and Cohen, W.: Statistical and Roentgenologic Analysis of Two Hundred Cases of Bone and Joint Tuberculosis, *Quart. Bull. Sea View Hosp.* 6:148-175 (Jan.) 1941.



resembles chronic nonspecific osteomyelitis. Tuberculous lesions of the membranous bones usually appear as punched-out areas, and the diagnosis can be confirmed only by biopsy. A valuable aid in the diagnosis of shoulder, knee, ankle and especially elbow joint tuberculosis is the presence of punched-out lesions in the shaft of the long bones adjacent to the involved joint.

The following summary is that of a histologic study by Cohn<sup>222</sup> of tuberculosis of the spine:

Histologic data from a study of 13 cases of tuberculous spondylitis are presented.

The intervertebral disk is attacked early in the course of the disease. The fibrocartilage and nucleus pulposus are destroyed before the hyaline portion of the disk.

The intervertebral disk may be invaded either directly from the contiguous subchondral marrow spaces or from the longitudinal ligaments after these have been invaded by the tuberculous process.

Areas of regenerating osseous and hyaline cartilaginous tissues are found in the reparative stages.

Obliterative endarteritis is a frequent finding in active foci.

The tuberculous process may extend from one body to another along the longitudinal ligaments.

[ED. NOTE: The preceding studies as well as the one by Cleveland and Bosworth reported at the meeting of the American Academy of Orthopaedic Surgeons in January 1942 show convincingly that tuberculosis of the spine is much more frequently multiple than was heretofore supposed. There is no doubt that ordinary roentgen studies frequently fail to demonstrate lesions in the bodies of vertebrae, especially when there has been no collapse of the body or thinning of the intervertebral disk. The use of the laminagraph at the New York Orthopaedic Dispensary and Hospital, New York, has resulted in the detection of lesions which were not shown in ordinary roentgenograms.

It seems much more logical and in accordance with the known facts to assume that the destruction of the intervertebral disk is secondary to that of the adjoining bodies than that a primary infection of cartilage occurs.]

*Urinary Complications.*—Colombani<sup>223</sup> found that of a total of 1,328 patients with osteoarticular tuberculosis observed from 1923 to 1939 at the Heliotherapeutic Institute of Codivilla, Italy, 224, or 16.9 per cent, had disease of the urinary system. Among these, 71, or 31.7 per cent (5.4 per cent of all the patients), had renal tuberculosis; 59, or 26.3 per cent (4.4 per cent of all the patients), had degenerative renal disease; 12, or

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222. Cohn, B. N. E.: Tuberculous Spondylitis: Histologic Study, *Arch. Path.* **32**:641-650 (Oct.) 1941.

223. Colombani, S.: Frequency of Urinary Complications in Tuberculous Osteoarthrititis, *Chir. d. org. di movimento* **26**:175-186 (Sept.) 1940; abstracted, *Internat. Abstr. Surg.* **73**:463, 1941; in *Surg., Gynec. & Obst.*, November 1941.

5.4 per cent (0.9 per cent of all the patients), had symptoms suggesting renal tuberculosis which, however, could not be diagnosed; 24, or 10.7 per cent (1.8 per cent of all the patients), had disorders of the urinary system of long standing which did not allow the diagnosis of tuberculosis of the kidney or of some other part of the system but suggested it; 58, or 25.9 per cent (4.4 per cent of all the patients), had temporary disorders of the kidneys or of the urinary passages.

Of the 224 patients with disease of the urinary system, 76, or 33.9 per cent, had died at the time of writing; in 29, or 13.0 per cent, the condition is aggravated; in 13, or 5.8 per cent, it has remained stationary; in 37 or 16.5 per cent, it has improved; in 11, or 4.9 per cent, it is cured, and in 58, or 25.9 per cent, there seem to have been only temporary disorders which in general have not interfered with the course of the osteoarticular disease. The aggravated and the stationary conditions of patients with disease of the urinary system have always led to an unfavorable prognosis.

Cultural and biologic studies of the urinary sediment are indicated in every case in which pathologic elements are present in the urine and in which even the slightest disturbance is found in the renal function. Only by such studies is it possible to diagnose and cure renal tuberculosis.

Webster<sup>224</sup> reports that among 64 adult subjects with bone and joint tuberculosis 32, or 50 per cent, were found by cultural method to be discharging tubercle bacilli of the human type in the urine. Findings except in 4 instances were the result of a single test. Of the 32 patients with bacilluria only 10 had urinary tract symptoms; 18 of the 22 symptomless patients presented red blood cells or excess leukocytes or both in the urine, and 4 provided no signs. Cultural investigation of the urine of 18 children affected by tuberculosis of bone resulted in recovery of tubercle bacilli in 6 instances, all 6 patients displaying clinical signs and symptoms indicative of involvement of the urinary tract.

In another group of 117 adult patients with clinical pulmonary tuberculosis 30, or 26.5 per cent, exhibited tuberculous bacilluria. Symptoms referable to involvement of the urinary tract were present in only 11 cases. A critical analysis of the literature convinces the author that the theory of excretory bacilluria is untenable, and he states that the presence of tubercle bacilli in the urine necessarily implies tuberculous infection of the kidney.

[ED. NOTE: One of us (A. D. S.) believes that these articles are important in calling attention to the frequency with which tubercle

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224. Webster, R.: Studies in Tuberculosis: Symptomless Tuberculous Bacilluria as Observed in Subjects of Osseous and Pulmonary Tuberculosis, M. J. Australia 2:217-221 (Aug. 30) 1941.

bacilli are found in the urine of patients with joint tuberculosis whenever a systematic search is made for them. R. I. Harris, of Toronto, reported a similar experience some time ago. Whether every patient whose urine contains tubercle bacilli has a surgical lesion of the urinary tract is another matter. Although it may be true that the bacilli cannot get into the urine without the presence of a lesion in the kidneys, it seems from experience that some of these lesions must heal spontaneously.]

*Gland Biopsy.*—Gellman<sup>225</sup> states that thirty-four regional gland biopsies were performed in a series of 23 cases of bone and joint disease. In 7 cases of nontuberculous conditions all cultural tests gave negative results, and none of the pathologic reports contained evidence of tuberculosis except in 1 case of recurrent synovitis of the knee in which the impression from the sections alone was possible tuberculous adenitis. In 4 cases of tuberculosis of the hip inguinal gland biopsies were not a satisfactory aid in diagnosis. In 12 cases a total of sixteen inguinal, axillary and epitrochlear regional gland biopsies were performed for tuberculous lesions in the following locations: the foot (one), the ankle (two), the lower part of the leg (two), the knee (seven), the wrist (one), the sternum (two) and the rib (one). The glandular biopsy test is said to have given fifteen positive reactions, or 93.75 per cent. (One case in which the histologic diagnosis was probable tuberculous adenitis is included.) In 5 of the cases control examination of inguinal lymph nodes from the opposite apparently unaffected lower extremity did not yield evidence of tuberculosis in 4 cases and did show evidence in 1 case in which a skin tuberculid was suspected. The author has found regional glandular biopsy to be a valuable diagnostic aid.

Agerholm-Christensen<sup>226</sup> recommends biopsy of regional lymph nodes in cases of chronic disease of bones and joints in which the course is in doubt on the basis of literature quoted and 1 case of his own. He resected a tuberculous metatarsophalangeal joint in a 30 year old woman and found tuberculosis in distal crural lymph nodes removed at the same time.

[ED. NOTE: Increasing experience seems to show that the regional lymph nodes are frequently involved in cases of joint tuberculosis. The finding of such nodes gives strong confirmation of the presence of tuberculosis in the joint but does not establish the diagnosis with absolute certainty. We still are of the opinion that for this reason biopsy of the joint tissue is the preferred method in doubtful cases.]

225. Gellman, M.: Regional Glandular Biopsy in Diagnosis of Bone and Joint Tuberculosis, *Bull. School Med. Univ. Maryland* 25:135-149 (Jan.) 1941.

226. Agerholm-Christensen, J.: Biopsy of Lymph Glands in Chronic Diseases of Bones and Joints: Diagnostic Value in Tuberculosis, *Ugesk. f. læger* 103:214-215 (Feb. 13) 1941.

*Experimental.*—Yegian and Halley<sup>227</sup> report inoculating virulent tubercle bacilli into subcutaneous fibrous tissue-lined channels resulting from six, thirty and sixty day implantation of rubber tubes into interscapular regions of 61 guinea pigs, some being sensitized by previous inoculation with tubercle bacilli of attenuated virulence. In animals killed one to seven days later axillary and inguinal lymph nodes revealed tubercle bacilli as determined by animal inoculation tests in 34 of 36 non-sensitized animals and in 21 of 25 sensitized ones. The conclusion is drawn that tubercle bacilli pass through fibrous tissue which is analogous to fibrous tissue present in the capsule of the tubercle.

*Tuberculous Rheumatism.*—Kling and Levine<sup>228</sup> report an interesting case of a condition which they believe to have been tuberculous polyarthritis resembling rheumatoid (atrophic) arthritis. They conclude that a mild type of tuberculous polyarthritis does occur, and they reach this conclusion on the basis of a detailed case history, a review of their own material and a review of the literature. [ED. NOTE: The rarity of rheumatoid arthritis in association with cases of proved joint tuberculosis casts grave doubt on the actuality of any such condition as tuberculous arthritis as originally described by Poncet. In a series of several thousand cases of joint tuberculosis observed at the New York Orthopaedic Dispensary and Hospital, New York, only 1 such case occurred, and it is believed that this was a coincidence.]

*Operative Procedures.*—Farill<sup>229</sup> reports 18 cases of tuberculosis of the hip in which operation was done by a method which he has devised. The patients are treated by preliminary rest until the disease apparently has subsided. A plaster spica then is applied with the hip in the desired position, and the operation is performed through a window in the plaster. It consists in driving a prism-shaped tibial graft through the head and the neck of the femur into the acetabulum, apparently without exposure of the hip joint itself. Farill speaks of the simplicity and safety of the operation and states that of the 14 patients followed for more than one year bony ankylosis was obtained in 12 (intra-articular in 6 and extra-articular in 6). Fibrous union occurred in 1, and the other patient died. [ED. NOTE: Although the operation appears to be simple and the early results in this small series are good, it seems doubtful whether in a large number of cases union could be expected to follow the introduction of a graft

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227. Yegian, D., and Halley, H. J.: Permeability of Fibrous Tissue to Tubercle Bacilli, *Am. Rev. Tuberc.* **44**:619-623 (Nov.) 1941.

228. Kling, D. H., and Levine, M. A.: Nondestructive Tuberculous Polyarthritis Versus Tuberculous Rheumatism (Poncet): Report of a Case, *Arch. Surg.* **42**:965-967 (May) 1941.

229. Farill, J.: Arthrodesis in Therapy of Tuberculous Coxitis of the Hip, *Gac. méd. de Mexico* **71**:172-202 (April 30) 1941.

through the diseased area of the joint. It has been our experience that whenever a bone graft is passed through or penetrates the area of disease it is absorbed or becomes loose.]

King and Richards<sup>230</sup> describe a technic for arthrodesis of the knee joint in cases of tuberculosis in young children. Tibial grafts are implanted into the patella in two stages, connecting this with the femur and the tibia. A brace is used for several years. Bony union occurred across the joint in only 1 of 4 cases. [ED. NOTE: This is an ingenious operation, but its superiority over removal of the joint cartilage seems doubtful.]

Bosworth and Haines<sup>231</sup> review several surgical technics employed on 85 patients with tuberculosis of the spine. A comparison of the method used in doing these fusions reveals that 60 were done by a modified Hibbs procedure in which bone chips and an osteoperiosteal graft from the tibia were used, that 10 were done by a modified Hibbs procedure in which extra bone from the ilium was used and that 15 were done by the original Hibbs procedure.

In the group of fusions done with osteoperiosteal grafts, pseudoarthroses developed in 15 per cent as compared with 10 per cent of those in which iliac bone was used and 9 per cent for those in which no extra bone was used.

There seems to be no advantage in using an extra disfiguring tibial incision.

[ED. NOTE: From these statistics it appears that the best results are obtained when the original Hibbs spine fusion is performed.]

*(To Be Continued)*

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230. King, D., and Richards, V.: Extra-Articular Arthrodesis of Knee Joint, *Am. J. Surg.* **53**:208-214 (Aug.) 1941.

231. Bosworth, D., and Haines, K.: Results of Spine Fusions: Critical Review of Several Surgical Techniques, *Quart. Bull. Sea View Hosp.* **6**:176-180 (Jan.) 1941.

## PROTHROMBIN AND HEPATIC FUNCTION

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It is now well established that prothrombin is continuously formed in the normal liver in the presence of adequate vitamin K. In 1938 Warner<sup>1</sup> observed that partial hepatectomy in the rat resulted in a decrease in the prothrombin content of the blood. Warren and Rhoads<sup>2</sup> reported in 1939 that after hepatectomy in dogs the plasma prothrombin fell to less than 20 per cent of normal within twelve to eighteen hours. Other evidence implicating the liver as a site of prothrombin production has been presented by many workers.<sup>3</sup> These investigators produced damage to the liver by giving animals various hepatoxins and observed a fall in plasma prothrombin.

There is also ample evidence at hand which points to the liver as the source of prothrombin in man. In patients with hepatic disease the prothrombin level is frequently down, and the giving of vitamin K to these patients either does not alter the prothrombin or does so slowly.<sup>4</sup> This

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This work was aided by grants from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, *J. Exper. Med.* **68**:831-835 (Dec.) 1938.

2. Warren, R., and Rhoads, J. E.: The Hepatic Origin of Plasma Prothrombin, *Am. J. M. Sc.* **198**:193-197 (Aug.) 1939.

3. Cullen, S. C.; Ziffren, E. S.; Gibson, R. B., and Smith, H. P.: Anesthesia and Liver Injury, *J. A. M. A.* **115**:991-993 (Sept. 21) 1940. Lord, J. W., Jr.: Effect of Trauma in the Liver on Plasma Prothrombin, *Surgery* **6**:896-898 (Dec.) 1939. Allen, J. G.; Kable, V., and Livingstone, H.: Effects of Anesthetic Agents on Prothrombin Concentrations in Experimental Animals, *Anesth. & Analg.* **20**: 156-159 (May-June) 1941.

4. (a) Pohle, F. J., and Stewart, J. K.: Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, *J. Clin. Investigation* **19**:365-372 (March) 1940. (b) Wilson, S. J.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, *Proc. Soc. Exper. Biol. & Med.* **41**:559-561 (June)

(Footnote continued on next page)

response is in sharp contrast to the rapid return of prothrombin to normal in patients with obstructive jaundice or biliary fistula. In the group with primary liver damage the reduced prothrombin is not due to inadequate vitamin K but to the inability of the liver to utilize the vitamin and form prothrombin.

Attention has recently been focused on hepatic function and prothrombin deficiency in an attempt to correlate liver disease with the prothrombin content of the blood. Wilson <sup>4b</sup> concluded that the prothrombin time was closely correlated with the excretion of hippuric acid of patients with liver disease. These results have not been generally confirmed.<sup>5</sup> Most workers are agreed that a crude relation may exist between hippuric acid excretion and blood prothrombin but that the extent of hepatic impairment as reflected by these two values is seldom in close agreement. Moreover, prothrombin production is but one of many functions of the liver, and experience has shown that these various functions are seldom, if ever, equally affected by hepatic injury. This fact serves to limit prothrombin deficiency as a measure of quantitative liver damage.

In 1940 we called attention to the fact that prothrombin deficiency resulting from the faulty absorption of vitamin K, as in cases of biliary fistula or obstructive jaundice, responded rapidly to vitamin K therapy, while prothrombin deficiency from primary liver damage either failed to respond to the vitamin or did so at a slow rate.<sup>6</sup> These observations formed the basis for a subsequent report that same year, in which we suggested that one could differentiate between intrahepatic and obstructive jaundice by the prothrombin response obtained when vitamin K and bile salts were administered.<sup>4a</sup>

In cases of extrahepatic obstructive jaundice the decreased prothrombin in the blood returns to the normal level in twenty-four to thirty-six hours after the oral administration of vitamin K and bile salts. A more prompt response may be obtained by the parenteral administration of suitable preparations. On the other hand, when reduction of

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1939. (c) Allen, J. G.; Julian, O. C., and Dragstedt, L. R.: Use of Serial Dilutions in Determination of Prothrombin by the One-Stage Technic, *Arch. Surg.* **41**:873-878 (Oct.) 1940. (d) Allen, J. G., and Julian, O. C.: Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, *ibid.* **41**:1363-1365 (Dec.) 1940.

5. Kark, R.; White, F. W.; Souter, A. W., and Deutsch, E.: Blood Prothrombin Levels and Hippuric Acid Excretion Liver Function Test in Liver Disease, *Proc. Soc. Exper. Biol. & Med.* **46**:424-426 (March) 1941. Lucia, S. P., and Aggeler, P. M.: The Influence of Liver Damage on the Plasma Prothrombin Concentration and the Response to Vitamin K, *Am. J. M. Sc.* **201**:326-340 (March) 1941. Allen, J. G.: Unpublished data.

6. Allen, J. G., and Julian, O. C.: Clinical Use of a Synthetic Substance Resembling Vitamin K, *Arch. Surg.* **40**:912-916 (May) 1940.

prothrombin is due to impairment of function and organic liver damage, either no response is secured by vitamin K therapy or the recovery is markedly delayed and incomplete.

Since our original report on this phase of the problem, reports by Andrus and Lord,<sup>7</sup> Olwin<sup>8</sup> and Kark and Souter<sup>9</sup> have confirmed our

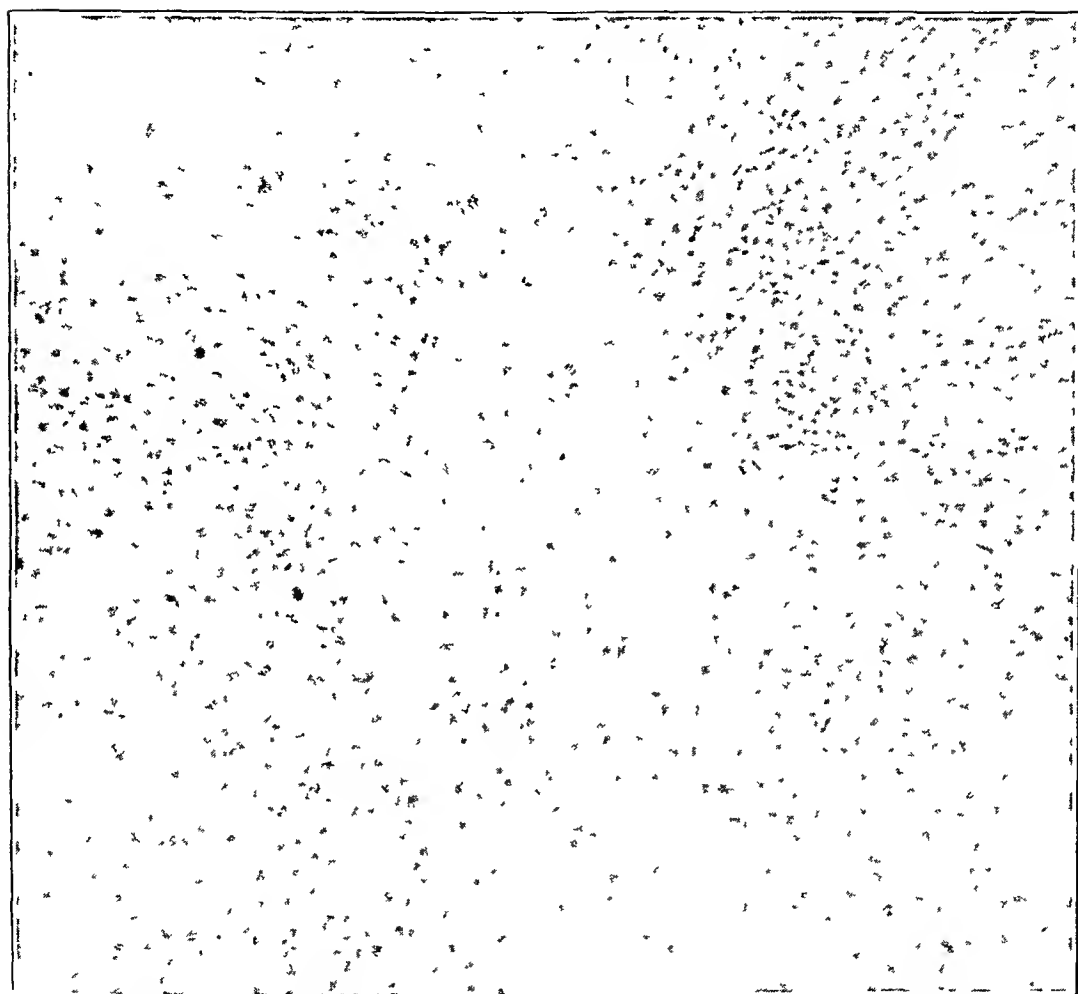


Fig. 1 (case 2, table 1).—Photomicrograph of the liver of a patient with obstructive jaundice and extensive secondary liver damage whose prothrombin deficiency was readily corrected with vitamin K.

7. Lord, J. W., and Andrus, W. W.: Differentiation of Intrahepatic and Extrahepatic Jaundice, *Arch. Int. Med.* **68**:199-210 (Aug.) 1941.

8. Olwin, J. H.: Differentiation of Surgical Jaundice from Severe Damage of the Liver (Subacute Yellow Atrophy) Clinically Simulating It, *Arch. Surg.* **43**: 633-644 (Oct.) 1941.

9. Kark, R., and Souter, A. W.: Response to Vitamin K: Liver Function Test, *Lancet* **2**:693-696 (Dec. 6) 1941.



observations and have indicated also the significance of the prothrombin responses to vitamin K in the jaundiced patient. This prothrombin response to vitamin K has now been used in this clinic for two years as a diagnostic procedure. Other cases to be presented here have now been studied; the results obtained in these extend and confirm our previous report.

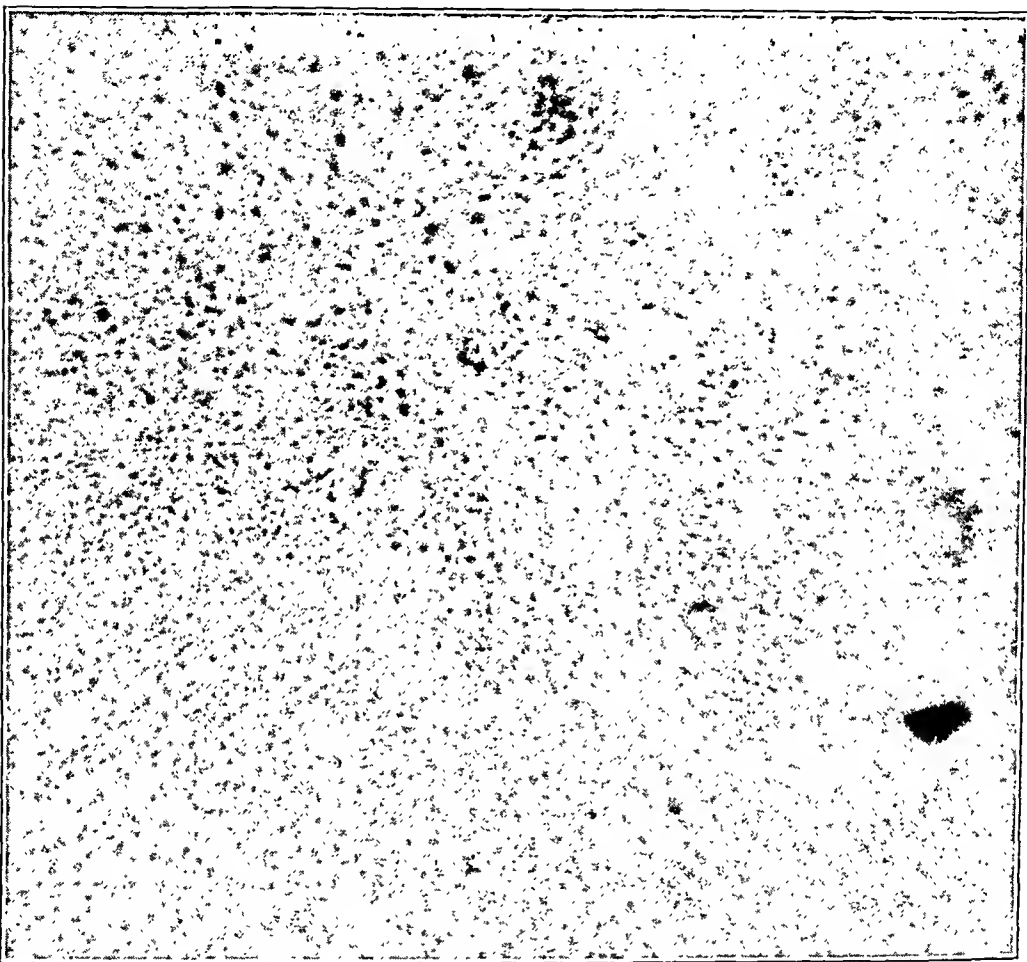


Fig. 2 (case 6, table 1).—Photomicrograph of the liver of a patient with obstructive jaundice and extensive secondary liver damage whose prothrombin deficiency was readily corrected with vitamin K.

#### REPORT OF CASES

*Seven Patients with Obstructive Jaundice; Sections of the Liver Were Made Either at Operation or at Autopsy (table 1).*

CASE 2.—The patient had stricture of the common duct for four months. At autopsy a moderate degree of periportal fibrosis was present. This patient responded readily to vitamin K, indicating that the liver damage secondary to

obstruction of the common duct was not sufficient to impair the production of prothrombin.

CASE 4.—The patient died after drainage of the common duct for choledocholithiasis and stricture. The liver weighed 1,950 Gm. and was light yellow-gray. The cut surface showed enlarged lobules. Section displayed chronic pericholangitis with definite biliary cirrhosis. Parenchymal cells were flattened, and atrophic canaliculi were often plugged by inspissated bile.

TABLE 1.—*Rapid Prothrombin Response of Patients with Obstructive Jaundice to the Administration of Vitamin K*

Case	Diagnosis	Prothrombin (Per Cent)		Daily Dose of Vitamin K (Mg.)	Comments
		Initial	24 Hr. After Therapy		
1	Stone in the common duct	45	100	8*	Icterus
2	Stricture of the common duct	15	100	8*	Icterus
3	Fistula of the common duct	55	100	8*	.....
4	Stone in the common duct	43	100	8*	Icterus
5	Stone in the common duct	63	100	8*	Icterus
6	Carcinoma of the pancreas with obstruction of the common duct	33	100	8*	Icterus
7	Stone of the common duct	28	100	8*	Icterus
8	Fistula of the common duct	35	100	8*	.....
9	Carcinoma of the head of the pancreas	66	100	8*	Icterus
10	Carcinoma of the head of the pancreas	28	100	8*	Icterus
11	Carcinoma of the head of the pancreas	56	100	8*	Icterus
12	Stricture of the common duct	61	100	8*	Icterus
13	Stone in the common duct	82	100	8*	Icterus
14	Carcinoma of the common bile duct	43	100	8*	Icterus
15	Carcinoma of the ampulla of Vater	58	100	8*	Icterus
16	Duodenal ulcer	70	100	10†	Liver normal at operation; no icterus
17	Fistula of the common duct	55	100	10†	.....
18	Carcinoma of the head of the pancreas	86	100	10†	Icterus
19	Carcinoma of the head of the pancreas	74	100	10†	Icterus
20	Fistula of the common duct	56	100	100	.....
21	Carcinoma of the ampulla of Vater	54	100	10†	Liver 8 cm. below the costal margin; icterus
22	Stone in the common duct	45	100	10†	Liver palpable at the costal margin; icterus
23	Stone in the common duct	85	100	10†	Liver 5 cm. below the costal margin; icterus
24	Stone in the common duct	65	100	10†	Icterus
25	Carcinoma of the common duct	58	100	10†	Liver 6 cm. below the costal margin; icterus
26	Carcinoma of the common duct	65	100	10†	Icterus

\* Patient was given 2-methyl-1, 4-naphthoquinone.

† Patient was given tetrasodium 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester.

CASE 6.—The patient had carcinoma of the head of the pancreas with obstruction of the common duct for four weeks. There was postoperative stricture of the common duct. Postmortem section of the liver showed a moderate degree of portal cirrhosis.

CASE 10.—Carcinoma of the pancreas had completely infiltrated the gland and obstructed the common duct. After operation ascending cholangitis developed and terminated in multiple abscesses of the liver. The liver weighed 1,780 Gm. Prothrombin response to vitamin K was rapid before operation.

CASE 11.—Cholecystogastrostomy was performed for obstructive symptoms caused by carcinoma of the head of the pancreas. The liver showed a slight increase in fibrous tissue and round cell infiltration in the periportal areas.

CASE 15.—The patient had carcinoma of the ampulla of Vater and died with extension of the tumor into the pancreas and the hepatic ligament and with obstruc-

TABLE 2.—*Poor Prothrombin Response to Vitamin K of Patients with Advanced Liver Disease*

Case	Diagnosis	Prothrombin (Per Cent)			Daily Dose of Vitamin K (Mg.)	Comments
		Initial	24 Hr. After Treatment	72 Hr. After Treatment		
1	Cirrhosis	48	48	48	8*	Icterus
2	Cirrhosis	23	25	29	8*	Marked icterus; died on seventh day; diagnosis confirmed at autopsy
3	Cirrhosis	22	22	20	8*	Marked icterus; died on eighth day
4	Cirrhosis	35	33	30	8*	Slight icterus; died on fifteenth day
5	Cirrhosis	43	37	53	8*	Marked icterus; died on twenty-third day
6	Cirrhosis	58	63	60	8*	Icterus
7	Cirrhosis	58	60	65	8*	Icterus and ascites
8	Cirrhosis	80	82	85	8*	Icterus and ascites
9	Cirrhosis	65	60	57	8*	Icterus and ascites
10	Cirrhosis	65	68	64	8*	Icterus and ascites
11	Cirrhosis	52	52	57	10†	.....
12	Cirrhosis	78	..	75	10†	Clinically worse
13	Cirrhosis	75	80	93	10†	Ascites; no icterus
14	Cirrhosis	70	70	72	10†	Ascites; no icterus
15	Cirrhosis	40	43	48	10†	Ascites; no icterus
16	Cirrhosis	80	80	83	10†	Ascites; no icterus
17	Cirrhosis	80	80	80	10†	Ascites; no icterus
18	Banti's syndrome	81	83	95	8*	No icterus
19	Banti's syndrome	75	78	80	8*	No icterus
20	Banti's syndrome	04	00	56	8*	No icterus; died on the twenty-first day
21	Wilson's disease	78	64	61	8*	No icterus
22	Fatty infiltration with peritonitis	46	43	48	8*	Slight icterus; died on the thirty-third day
23	Multiple liver abscesses	57	56	54	8*	Marked icterus; died on the seventh day
24	Acute hepatitis	10	15	..	8*	Marked icterus; hemorrhagic diathesis; died on the fourth day
25	Acute hepatitis	48	34	50	8*	Marked icterus; died on the seventh day
26	Acute hepatitis	41	68	95	8*	Marked icterus
27	Metastatic carcinoma to the liver	57	62	100	8*	No icterus
28	Multiple liver abscesses	56	62	75	8*	Icterus
29	Multiple myeloma with large liver	62	62	61	8*	Liver 10 cm. below the costal margin
30	Banti's syndrome	64	66	75	8*	.....
31	Liver abscesses	75	68	60	8*	Died; multiple liver abscesses

\* Patient was given 2-methyl-1, 4-naphthoquinone.

† Patient was given tetrasodium 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester.

tion of the common duct. Marked jaundice was present. The liver weighed 2,050 Gm. Histologic studies showed marked dilatation of biliary canaliculi, focal necrosis and cellular increase in triads.

CASE 25.—The patient was jaundiced during the course of the illness owing to carcinoma of the cystic duct involving the common duct. Autopsy disclosed that

the liver was bile stained and weighed 2,250 Gm. Section showed round cell infiltration, a moderate amount of fibrosis and marked dilatation of biliary canaliculi.

*Ten Patients with Jaundice Due to Hepatic Disease; Sections of the Liver Were Made Either at Operation or at Autopsy (tables 2 and 3).*

CASE 1.—Biopsy of the liver disclosed extensive fatty infiltration of the parenchyma.

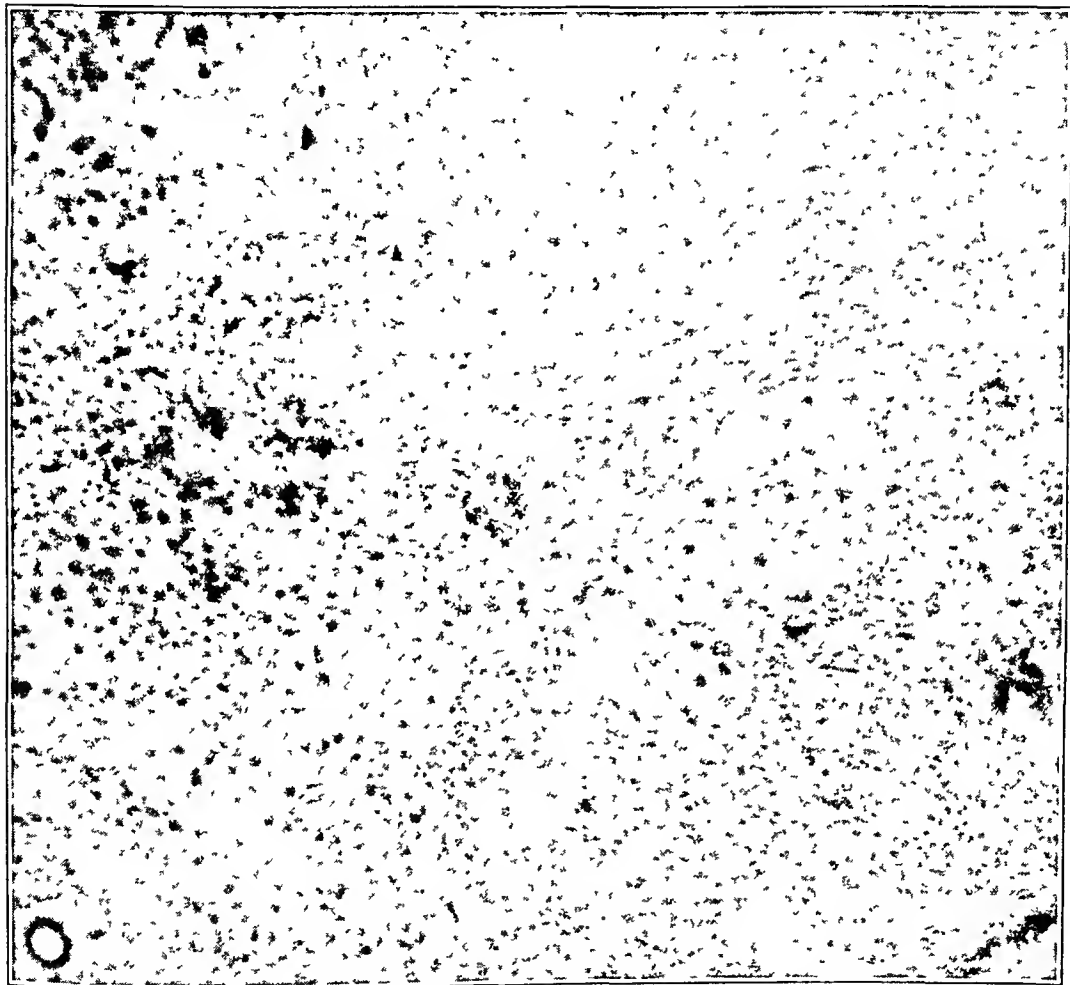


Fig. 3 (case 2, table 2).—Photomicrograph of the liver of a patient with extensive cirrhosis in whom vitamin K exerted no effect on prothrombin deficiency.

CASE 4.—At autopsy the liver weighed 1,470 Gm., showing changes of chronic passive congestion. Histologically, not much damage was seen. There was marked evidence of chronic passive congestion.

CASE 5.—The patient showed minimal icterus. Autopsy was done. The liver weighed 1,500 Gm. Sections showed slight periportal fibrosis. The intrahepatic ducts were not dilated.

CASE 7.—The patient had been jaundiced one year and had had ascites for three of four months. Autopsy disclosed advanced portal cirrhosis. All sections showed marked fibrosis with evidence of regeneration.

CASE 19.—The patient had Banti's syndrome and ascites. The liver weighed 1,910 Gm. and had a granular surface; the cut surface showed marked perilobular fibrosis. Histologic study showed moderate portal cirrhosis and extensive areas of recent and old necrosis.

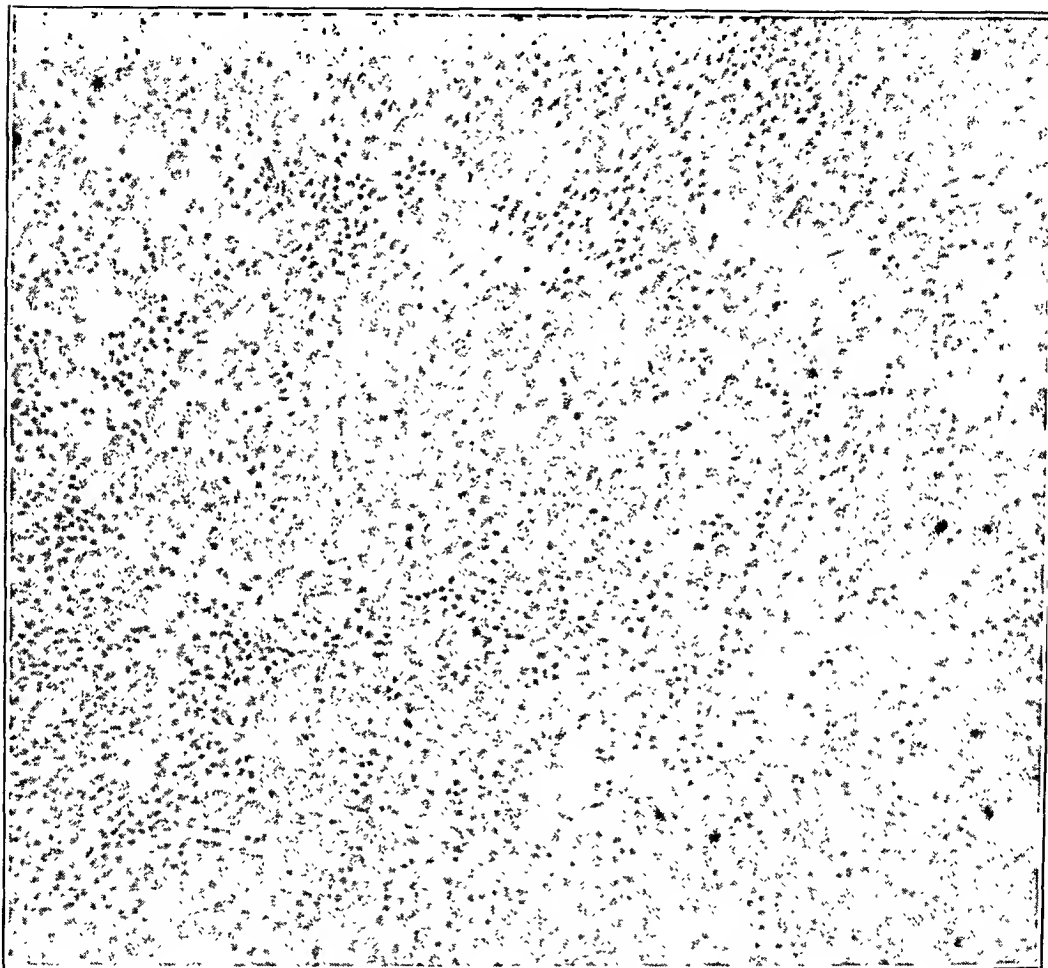


Fig. 4 (case 5, table 2).—Photomicrograph of the liver of a patient with extensive cirrhosis in whom vitamin K exerted no effect on prothrombin deficiency.

CASE 22.—Biopsy of the liver disclosed extensive parenchymatous degeneration. The liver was small.

CASE 23.—The patient died with multiple interstitial liver abscesses following drainage of the common duct (choledocholithiasis). At autopsy the liver weighed 2,200 Gm. and was purple-bronze in color. Section showed moderate fatty degeneration, early fibrosis of biliary distribution and marked round cell infiltration about the triads.

CASE 28.—In this case there were multiple liver abscesses, localized peritoneal abscesses and subdiaphragmatic abscess following rupture of the gallbladder due to carcinoma of the head of the pancreas. The obstruction was found to be incomplete at autopsy. The liver showed multiple small abscesses.

CASE 31.—The patient died of multiple liver abscesses following appendectomy complicated by septic thrombophlebitis. Ascites developed before death. The liver weighed 3,300 Gm. and was extensively destroyed by abscesses and intervening necrosis of the parenchyma.

CASE 1 (table 3).—The patient had a history of alcoholism, and biopsy of the liver revealed fatty infiltration of the parenchyma and some hyalinization.

TABLE 3.—*Patients with Clinical Evidence of Liver Damage and Prothrombin Deficiency Who Have Received Vitamin K Continuously*

Case	Diagnosis	Initial Determination	Prothrombin (Per Cent)				Comment	
			Subsequent Determination					
1	Cirrhosis	52	60 (5 weeks)	63 (8 weeks)	78 (12 weeks)	100 (56 weeks)	Gradual clinical improvement; paracenteses became unnecessary	
2	Cirrhosis	55	72 (3 weeks)	100 (8 weeks)		100 (59 weeks)	Clinically excellent on medical regimen; no ascites for 6 mo.	
3	Cirrhosis	74	55 (3 weeks)	60 (6 weeks)	55 (8 weeks)	45 (25 weeks)	63 (19 weeks)	Still unimproved; continued to require abdominal paracenteses weekly; died at end of 6 mo.
4	Cirrhosis	70	75 (3 weeks)	55 (5 weeks)	37 (7 weeks)			Died at end of 2 mo.; subcutaneous ecchymoses

#### COMMENT

The patients whose cases are presented here were divided into three groups according to causation of the prothrombin deficiency. In all cases the therapeutic tests given with vitamin K were the same. These tests consisted either of oral administration of 8 mg. of 2-methyl-1, 4-naphthoquinone (menadione) with 2.5 Gm. of bile salts per day or of intravenous injection of 10 mg. of the water-soluble compound tetrasodium 2-methyl-1, 4-naphthoquinone diphosphoric acid ester.<sup>10</sup> The prothrombin activity was determined at the end of twenty-four hours by the serial dilution one stage technic.<sup>4c</sup> The first group (table 1) consisted of 21 patients with obstructive jaundice, 4 with complete external biliary fistula, 2 with esophageal carcinoma and 1 with gastric ulcer under treatment; the last-named 3 had inadequate food intake, and all had prothrombin deficiency. The second group consisted of 31 patients with prothrombin deficiency and jaundice due to intrahepatic disease. The third group was composed of 4 patients without jaundice who presented primary prothrombin deficiency associated with cirrhosis of the liver and ascites.

10. The compound used was synkovite-Roche.

Specimens of the liver were obtained in a number of the cases in each group at autopsy or at laparotomy. The histologic data are reported in the accompanying protocols. Photomicrographs of 4 of the specimens are presented (figs. 1, 2, 3 and 4).

In the cases shown in table 1 there was one common factor—the inadequate absorption of vitamin K. The factor responsible for this inadequate absorption was: (1) absence of bile salts from the intestine in 21 cases of obstructive jaundice of proved causation and in 4 cases of complete external biliary fistula or (2) inadequate ingestion of foods containing vitamin K in 3 cases. It was characteristic of the cases in this group that the administration of vitamin K by a method providing certain absorption caused an immediate elevation in the plasma prothrombin level. These were consecutive cases of obstructive jaundice observed at the University of Chicago Clinics, and in none did the response to vitamin K fail to occur.

The second group included 17 patients with cirrhosis of the liver and jaundice, 4 with the so-called Banti syndrome and mild jaundice, 5 with extensive destruction of the liver due to abscesses and 3 with acute hepatitis or catarrhal jaundice. The characteristic of this entire group was that the depressed plasma prothrombin was either not affected or only slowly elevated by the administration of vitamin K. As contrasted with the first group, the common factor here was primary liver disease of varied causation associated with jaundice.

Our previous report of a smaller but similar series of cases indicated that the plasma prothrombin determination in relation to a therapeutic trial with vitamin K provides a reliable differentiation between intrahepatic and obstructive jaundice.<sup>4d</sup> The present, more extensive series confirmed the earlier observations. Although a certain amount of liver damage usually accompanies obstructive jaundice even of a short duration, we have not yet encountered a case in which this damage was sufficient to prevent the prompt response of prothrombin to therapy with vitamin K. However, such cases will undoubtedly occur when untreated obstruction has produced sufficient liver damage, i. e. biliary cirrhosis. In such a case, the failure of prothrombin to respond to a therapeutic test would lead to an erroneous diagnosis of primary intrahepatic disease and obscure the basic pathologic condition itself, possibly amenable to operation. In this regard it is of interest that 1 of our patients had post-operative stricture of the common duct with jaundice of six months' duration and showed severe liver damage at autopsy but nevertheless displayed a rapid response to therapeutic test (case 3).<sup>11</sup>

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11. We recently observed a 55 year old patient on whom cholecystectomy was performed for cholelithiasis in January 1941 and who became icteric in April 1942. Intermittent chills and fever continued, and by June 1942 ascites had developed. This patient, when seen in this clinic, had an icteric index of 42 units and a prothrombin level of 50 per cent. In spite of adequate vitamin K therapy the patient's prothrombin had risen to only 68 per cent after one week's treatment. At operation

The question arises: Is it possible to anticipate the extent of the liver damage from the response to vitamin K in a given patient with liver disease? In this regard we have examined the microscopic pathologic picture present in the liver in 17 cases in both groups (cases of tables 1 and 2). Brief descriptions of the microscopic pathologic picture of the liver in 6 cases of group 1 and 11 of group 2 have been presented. No correlation was observed between the degree of damage shown in the microscopic sections or in the gross appearance of the liver and the initial prothrombin level or the rate and degree of prothrombin response. These observations led us to conclude that the degree of prothrombin deficiency with liver disease does not reflect the extent of the injury to the liver and that in this sense prothrombin deficiency is not a reliable measure of liver function. Moreover, we have observed patients with demonstrable primary liver disease in whom the plasma prothrombin was found to be normal.

However, in 4 cases presented in table 3 the prothrombin level under continuous adequate vitamin K intake seemed to reflect the clinical course of the disease in the individual patient. Two of the patients (cases 1 and 2) with hepatic cirrhosis and ascites gradually improved on medical management, requiring less frequent paracenteses, and were finally able to resume normal activity. In these 2 patients the prothrombin level rose over a period of eight and twelve weeks from 52 and 55 per cent to normal. The other 2 patients showed the reverse, the level going from 74 and 70 per cent to 45 and 32 per cent; both finally died of cirrhosis. Sections of the liver were obtained from all 4 patients of this group. Though few in number, these patients provided a strong suggestion that the prothrombin level (always supposing an adequate intake of vitamin K) provides a good index to the course of the disease for that particular patient.

#### CONCLUSIONS

The prothrombin determination in connection with a therapeutic trial of vitamin K therapy constitutes an accurate means of differentiation between intrahepatic and extrahepatic jaundice.

The prothrombin determination with or without trial vitamin therapy is not qualified as a quantitative test of liver function.

Serial prothrombin determinations over a period of time on a patient with hepatic disease may be a suitable index of the progress of the disease.

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two large stones were found in the common duct. A specimen of the liver was taken for biopsy, and *Bacillus typhosus* was cultured from it. Histologically, marked inflammatory changes were found in the periportal areas with an increase in the fibrous tissue.

This case serves to demonstrate the simultaneous occurrence of extensive liver disease and obstruction to the common duct in the same patient. In such cases diagnosis cannot be made by the prothrombin response to vitamin K.



# BENIGN TUMORS OF THE STOMACH

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Benign gastric tumors have received rather minor consideration in the literature compared to that accorded to ulcer and malignant lesions. Although sufficient reasons certainly justify this, several facts seem to warrant more than a mere academic acknowledgment of the benign

TABLE 1.—*Tumors of the Stomach Observed at Autopsy\**

Malignant		Benign	
Adenocarcinoma.....	81	Polyp.....	14
Scirrhus carcinoma.....	12	Fibroma.....	8
Medullary carcinoma.....	8	Papilloma.....	4
Colloid.....	4	Leiomyoma.....	2
Carcinoma simplex.....	4	Fibromyoma.....	2
Linitis plastica.....	2	Adenoma.....	2
Krukenberg.....	2		
Total malignant tumors.....	113 (78%)	Total benign tumors.....	32 (22%)
Total tumors of the stomach.....		145	
Number of autopsies, 1930 to 1934 inclusive.....		4,413	
Autopsies at which stomach tumors were observed.....		3.28%	
Autopsies at which malignant stomach tumors were observed.....		2.66%	
Autopsies at which benign stomach tumors were observed.....		0.72%	

\* Autopsies done at Bellevue Hospital, 1930-1934 inclusive.

tumors. These facts may be briefly enumerated: 1. The reported clinical rarity is certainly relative and due in part to lack of recognition. 2. Errors in diagnosis have too commonly led to ill timed and unnecessarily radical operations. 3. Critical illness frequently results from not unusual strangulation, pyloric obstruction or hemorrhage. 4. Malignant degeneration of certain types occurs rather often. Since these facts, variously emphasized by others, have been encountered in our own experience, it seems advisable to report this review of the situation at Bellevue Hospital, New York.

Various authors have differed widely in estimating the relative frequency of benign and malignant gastric neoplasms. The rather sharp contrast between the figures obtained from autopsies and those obtained from clinical examinations in this study clearly illustrates one basis for such diversity of opinion.

In 4,413 autopsies done at Bellevue Hospital during five years (1930-1934), 22 per cent of all gastric tumors observed were benign (table 1).

This figure closely approximates the 22.8 per cent in the 11,000 autopsies of Stewart<sup>1</sup> at Leeds, England, and the 26.2 per cent of Rigler and Ericksen<sup>2</sup> in 6,242 autopsies at the University of Minnesota (table 3).

Comparison of the records of 76,077 adult surgical and medical patients admitted to the hospital during three years and seven months (Jan. 1, 1935, to Aug. 1, 1938) revealed that 456 had been operated on for gastric tumors. In 450 of the cases the neoplasms were malignant, and in 6 they were benign. Thus 1.3 per cent of all gastric tumors with symptoms or signs sufficient to warrant operation were benign (table 2).

TABLE 2.—*Tumors of the Stomach Among Patients Admitted to the Hospital\**

Total patients admitted (adult, medical and surgical).....	76,077
Total malignant gastric tumors.....	450 (98.7%)
Total benign gastric tumors.....	6 (1.3%)
Adenoma.....	4
Fibromyoma.....	1
Leiomyoma.....	1

\* Patients admitted to Bellevue Hospital, Jan. 1, 1935, to Aug. 1, 1938. Of the patients admitted, 0.6 per cent had gastric tumors treated.

TABLE 3.—*Frequency of Benign Tumors Reported in the Literature*

Author	Material	Benign Tumors	Malignant Tumors	Ratio	Gastric Tumors, per Cent
Stewart <sup>1</sup> .....	11,000 autopsies	78	263*	3.3:1	22.8
Rigler and Ericksen <sup>2</sup> .....	6,242 autopsies	49	138	2.8:1	26.2
				(operative cases)	(operative cases)
Eusterman and Senty <sup>3</sup> .....	2,195 operative cases	27	2,168	78:1	1.3
	2,285 inoperative cases	..	4,480	165:1 (total)	
Dudley, Miscall and Morse..	4,413 autopsies †	32	113	3.5:1	22.0
	456 operative cases †	6	450	75:1	1.3
					(operative cases)

\* Carcinomas.

† See table 1.

‡ See table 2.

This operative incidence checks exactly with that in the larger group reported by Eusterman and Senty<sup>3</sup> (table 3).

At least part of the disparity between the figures obtained from autopsies and those obtained from clinical observations arises from the fact that only the symptomatic benign tumors come to operation. The majority of benign tumors may give few or no symptoms and may be

1. Stewart, M. J.: Observations on the Relation of Malignant Diseases to Benign Tumors of the Intestinal Tract, *Brit. M. J.* 2:567-569, 1929.

2. Rigler, L. G., and Ericksen, L. G.: Benign Tumors of the Stomach, *Radiology* 26:6-15, 1936.

3. Eusterman, G. B., and Senty, E. G.: Benign Tumors of the Stomach, *Surg., Gynec. & Obst.* 34:5-15, 1922.

completely overlooked during life. However, the general estimate that 0.5 to 5 per cent of all gastric tumors are benign is apparently too low. The figure is probably nearer 15 to 20 per cent. An interesting observation reported in the literature was that of Rieniets<sup>4</sup> at the Mayo Clinic. His diligent examination for only gastric leiomyomas in 200 consecutive autopsies revealed that there were such benign tumors in 16 per cent, frequently small and asymptomatic but still definite, and that malignant disease was present in 6 per cent.

At Bellevue Hospital the records of 76 microscopically examined benign gastric tumors have been collected from 21,026 cases in which autopsy was done in twenty-three years (June 1, 1915 to June 1, 1938) for all causes of death. The details of these cases recorded in tables 4 and 5 have been correlated with the reports of other authors. The variations apparent here were attributed previously by others to the lack of both or either complete microscopic diagnosis and uniform terminology among pathologists. This conclusion is warranted by our experience. However, in all reports mucosal polyps, papillomas and myomas constitute a real majority. Apparently the pylorus is more selectively involved, but no type of tumor displays any distinct predilection for any one portion of the stomach.

Sixty of the 76 patients had been observed sufficiently in the hospital for a complete clinical diagnosis to be made. Despite this, in not one case was the correct diagnosis made before death. Careful review of these 60 satisfactory records shows many interesting facts. Forty-two (70 per cent) of the 60 patients adequately followed were quiescent and asymptomatic. In addition, physical examination and laboratory work-up including roentgen studies were devoid of any positive findings indicative of gastric disease. All types occurred asymptotically throughout the stomach. Although clinical diagnoses covered a multiplicity of possibilities, the chief complaint was not referable to the stomach in any 1 of these 42 cases. Most patients had other causes substantiated by postmortem examination for any gastrointestinal symptoms. Furthermore, close check-up of postmortem reports failed to reveal evidence that these tumors might have been symptomatic during life, since gastritis, strangulation, ulceration, bleeding and obstructive prolapse were all absent.

In the light of this experience with 42 proved benign gastric tumors it is reasonable to state that these tumors frequently may remain asymptomatic for years without detriment to the person.

Such favorable conditions do not always prevail. Quiescence may be supplanted by activity with vague and atypical symptoms leading to confusion rather than clarity. This situation existed in the other 18 suffi-

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4. Rieniets, J. H.: The Frequency and Pathologic Aspects of Gastric Leiomyoma, *Proc. Staff Meet., Mayo Clin.* 5:364-366, 1930.

TABLE 4.—Correlation of Types of Benign Gastric Tumors Observed at Bellevue Hospital with Those Reported in the Literature

Authors	Cases	Single		Multiple		Myoma		Fibroma		Adenoma		Angioma		Dermoids and Cysts		Lipoma		Other Tumors	
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Bellevue Hospital *	76†	23	30.2	16	21.0	15‡	20.0	12	16.90	8	10.5	..	....	..	...	..	....	2¶	2.6
Eusterman and Senty *	27†	3	11.1	1	3.7	10	37.3	5	18.00	2	7.3	4	14.7	2	7.30	..	....	..	..
Judd, E. S., and Hoerner, M. T.: Am. J. Surg. 31: 427-430, 1920	50†	—	Excluded	—	—	35	70.0	8	16.00	3	6.0	3	6.0	Excluded	1	2.0	..	....	..
Halfour, D. O., and Henderson, E. P.: Ann. Surg. 85: 351-359, 1927	68†	14	24.1	4	6.8	23	39.6	..	....	4	6.8	4	6.8	3	5.10	..	....	6	10.3
Rigler and Eriksen *	49†	—	—	31	63.0	—	—	..	....	2	4.0	..	....	..	....	..	....	4	8.5
Stewart †	78†	27	34.5	20	25.6	22	28.2	..	....	..	....	..	....	..	....	5	6.4	4#	5.3
Ellison, E. L., and Wright, V. W., M.D.: Surg., Gynec. & Obst. 44: 101-172, 1925	560 (col-lected)	77	13.6	11	1.9	321	57.3	23	4.12	31	5.5	10	1.7	29	5.17	28	5.0	30	6.7
(personal)§	50	32	64.0	1	2.0	4	8.0	6	12.00	5	10.0	..	....	1	2.00	1	2.0	..	..
Mihnes, J. P., and Geschlecker, C. P.: Am. J. Cancer 28: 130-140, 1936	931 (col-lected)	271	29.0	16	1.7	344	37.0	42	4.50	42	4.5	15	1.6	38	4.10	32	3.4	130	14.2
(personal)	50	5	10.0	25	52.0	16	32.0	1	2.00	..	....	1	2.0	..	....	..	....	1	2.0
Percentage limits .....	—	—	—	—	14.8 to 66.0	—	8.0 to 57.3	2.0 to 18.0	4.5 to 10.0	4.5 to 10.0	1.6 to 14.7	2.0 to 7.3	2.0 to 6.4	..	..	..	..	..	..

\* A total of 21,026 autopsies were done at Bellevue Hospital between June 1, 1915, and June 1, 1938; the 76 cases in which benign tumors were observed represent 0.35 per cent of the autopsies.

† Tumors observed at autopsy.

‡ Tumors observed at operation.

§ Tumors observed at operation and autopsy.

¶ Leiomyoma, 4; fibroleiomyoma, 1; fibromyoma, 5; multiple myoma, 1; solitary myoma, 4.

# Fibroadenoma, 1; fibrolipoma, 1.

# Among 5,700 autopsies.

ently observed cases. In these cases the symptoms, the physical signs and the laboratory and roentgen studies failed to agree sufficiently to indicate the gastric lesion clearly. The benign tumors were not even mentioned in these cases, all being either incorrectly diagnosed or missed completely. Reasons for this evident confusion will be presented later in consideration of the operative cases.

The association of ulceration, gastritis and malignant disease with benign gastric tumors has easily recognized importance. In various series the following figures were reported: Ulceration either in the

TABLE 5.—*Distribution of Various Types of Benign Gastric Tumors Observed at Bellevue Hospital*

Location	Polyp	Myoma	Fibroma	Adenoma	Total	Percentage
Pylorus.....	15	6	2	6	29	47*
Media.....	14	7	3	1	25	39†
Cardia.....	4	2	3	1	10	14‡
Diffuse.....	6	0	4	0	10	
Unstated.....	0	1	0	1	2	
Total.....	39	16	12	9	76	

\* The percentage reported by E. S. Judd and M. T. Hoerner (Am. J. Surg. 31:427-430, 1936) was 66; that reported by J. F. Minnes and C. F. Geschickter (Am. J. Cancer 28:130-149, 1936) was 46.

† The percentage reported by Judd and Hoerner was 24; that reported by Minnes and Geschickter was likewise 24.

‡ The percentage reported by Judd and Hoerner was 10; that reported by Minnes and Geschickter was 30.

TABLE 6.—*Distribution of Asymptomatic Benign Tumors in Forty-Two Cases*

Location	Polyp	Fibroma	Myoma	Adenoma	Fibrolipoma	Total
Pylorus.....	8	2	0	2	0	12
Media.....	4	0	0	0	0	4
Cardia.....	4	2	2	0	0	8
Unstated.....	2	2	1	0	1	6
Multiple.....	8	1	0	0	0	9
Subserosal.....	0	1	2	0	0	3
Total.....	26	8	5	2	1	42

tumor or elsewhere in the stomach and the duodenum occurred in 15 to 46 per cent of the cases. Malignant degeneration had an incidence of about 25 per cent in the mucous polyps. Gastritis of all degrees has been repeatedly observed but frequently overlooked in pathologic reports unless of a severe grade. It is likely that many benign tumors remain asymptomatic until the onset of one or all of these complications. Table 7 details our figures in comparison with those of other series we have collected.

Ulcers of the stomach or the duodenum coexisted with benign gastric tumors in 11 cases, 3 of which may be cited: In case 39 there was fibromyoma at the cardia with multiple bleeding duodenal ulcers. In

case 15 there were multiple polyps of the fundus with acute gastric ulcers in this region. In case 46 there was ulcerated pyloric fibromyoma with acute gastric and duodenal ulcers, marked gastritis and massive hemorrhage.

The following short summaries of 3 cases of gastric carcinoma existing in benign tumors are of interest:

In case 33 the patient showed minimal gastric symptoms but had two gastric polyps in the pars media. A pedunculated tumor was

TABLE 7.—*Association of Ulcer and Malignant Disease with Benign Gastric Tumors in This Series and Various Series Reported in the Literature*

Authors	Cases	Ulcer		Associated Malignant Growth		Malignant Degeneration		Comment
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	
Benedict, E. B., and Allen, A. W.: <i>Surg., Gynec. &amp; Obst.</i> 58: 79-84, 1934	17	..	....	..	....	7	41.2	Specimens were obtained at operation in cases of polyp with fairly severe symptoms
Stewart <sup>1</sup> .....	47	..	....	..	....	13	27.6	Polyps observed at autopsy
Miller, T. G.; Ellason, E. L., and Wright, V. M. W.: <i>Arch. Int. Med.</i> 46: 841 (Nov.) 1930	23	..	....	..	....	8	35.0	Polyps examined
Minnes, J. F., and Geschickter, O. F.: <i>Am. J. Cancer</i> 28: 130-149, 1936	31	..	....	..	....	3	10.0	Polyps examined
Mills, G. P.: <i>Brit. J. Surg.</i> 10: 226-231, 1922	20	..	....	..	....	4	20.0	Polyps
Brunn, H., and Pearl, F.: <i>Surg., Gynec. &amp; Obst.</i> 43: 559-598, 1926	84	..	....	..	....	10	12.0	Collected cases of polyposis
Judd, E. S., and Hoerner, M. T.: <i>Am. J. Surg.</i> 31: 427-430, 1936	50	..	46.0					
Balfour, D. C., and Henderson, E. F.: <i>Ann. Surg.</i> 85: 354-359, 1927	58	..	17.0					
Dudley, Miscall and Morse, present report	76	11	15.8	2	2.6	10	13.0	Autopsy done in all cases
	39	..	....	..	....	9	23.0	Polyps observed at autopsy

reported as a simple mucous polyp, while the other, which was of the sessile type, showed definite carcinomatous degeneration with metastases to the mediastinal and regional lymph nodes.

In case 21 the patient with symptoms and signs sufficient for a clinical diagnosis of carcinoma had two distinct papillary adenomas at the pylorus. The sessile tumor, however, showed adenocarcinomatous degeneration with scattered peritoneal metastases.

In case 50 marked symptoms referable to the stomach showed a somewhat sessile pyloric papilloma with carcinomatous degeneration and metastases in the liver.

All 3 patients showed ulceration of the malignantly degenerating benign tumor but only in the more sessile tumors. Most important was the fact that in these 3 cases the condition progressed to the stage of metastatic malignant disease before any of the patients were forced into the hospital by gastric symptoms.

Two other cases merit citation: In case 7 the patient had a pedunculated polyp in the pars media with a large carcinoma of the greater curvature. In case 9 the patient had a pyloric mucous polyp associated with a papillary adenocarcinoma at the cardia on the lesser curvature. In neither of these cases was malignant degeneration of a benign tumor represented; rather the coexistence of benign and malignant lesions in the same stomach was shown.

Benign gastric tumors were associated with extragastric malignant lesions on only 3 occasions. In case 10 there was gastric leiomyoma with retroperitoneal fibrosarcoma. In case 45 there was gastric papilloma with prostatic adenocarcinoma. In case 65 there was gastric myoma with primary carcinoma of the liver.

Benign gastric tumors were associated with extragastric benign lesions only twice. In case 34 there was gastric polyp with sigmoidal polyp. In case 20 there were multiple fibromas of the stomach with a polyp in the ascending colon.

The practical difficulties of detailed diagnosis in such cases are readily evident, but the possibility of such complex association should not be forgotten. This is especially important when these previously undiagnosed lesions first come to light at operation, for radical revision of surgical procedure may then become imperative. The possibility of progression to the stage of metastatic malignant disease with little or no change in symptoms must be constantly realized.

The operative benign tumors, 32 cases of which have been collected in ten years, may now be considered. Although many records are too incomplete to warrant detailed tabulation as in the cases in which autopsy was done, certain facts deserve emphasis as operative and clinical experience.

The bare 30 per cent of tumors correctly diagnosed before operation compares rather unfavorably with the 65 per cent found more or less by accident. In the latter group, 50 per cent were labeled gastric carcinoma, while the other 15 per cent were called bleeding ulcers almost exclusively. Unquestionably an error of such magnitude demands that its causes be searched out. If this situation in the presence of obvious symptoms cannot be remedied, certainly no success must be expected in the larger relatively asymptomatic group. Such a survey was made and yielded this one essential fact, that the mistakes have usually emanated from inadequate appreciation of the clinical and laboratory characteristics of these tumors. The experience of this study seems to justify listing some facts more or less characteristic of benign gastric tumors.

The large majority of patients coming for treatment give a history of some protracted gastric disturbance. Past complaints, usually mild and irregular, most often lack the periodicity, the progression and other common attributes of ulcer or carcinoma. The patient has more or less neglected these symptoms until driven to the hospital by one of the more severe complications of pyloric obstruction, hemorrhage or strangulation. Without doubt this sudden transition from fairly good health with few symptoms to acute illness with alarming symptoms has been rather characteristic in our experience.

Gastric hemorrhage (occurring in 40 per cent of all cases) was the commonest initial symptom forcing patients to seek treatment. It generally resembled the massive bleeding of ulcer more closely than the slow weeping of carcinoma. Loss of blood was sudden and extensive enough in half of these cases to cause surgical shock with the hemoglobin content below 50 per cent. Such severe exsanguination occurred almost exclusively in patients with mucous polyps and more in persons with pedunculated than in those with sessile tumors. A few patients exhibited anemia with weakness secondary to slower bleeding. In only 4 of 12 cases was the correct diagnosis made, but proper attention to the antecedent history might well have increased this figure. Two of these patients died.

Pyloric obstruction was present in 10 cases, representing an incidence of about 30 per cent. It was either progressive or intermittent in character, dependent on the location and the type of tumor.

The sessile pyloric tumors accompanied by pylorospasm frequently produced persistent and progressive symptoms of obstruction. A roentgen filling defect with gastric residue was not unusual. In this they closely simulated carcinoma, even though, being small and intramural, they did not bleed or ulcerate as frequently.

The pedunculated and mobile benign tumors distant from the pylorus presented a contrasting picture. Symptoms of obstruction were definitely intermittent with attacks of nausea and vomiting being precipitated by prolapse to or through the pyloric ring. These bouts abated or ceased with recession of the tumor from the gastric outlet. (One patient with a pedunculated polyp had no symptoms while he was in the reclining position but complained of nausea and vomiting after meals in the erect position.) Roentgenograms varied. Gastric residue was reported only in the presence of prolapse. The filling defect was often replaced by bizarre regular circling of the mass by barium sulfate in either the duodenum or the stomach. Subsequent studies frequently showed nothing, particularly in an asymptomatic period after return of the tumor to its normally higher position.

In review, the findings of roentgen studies in cases of both the pedunculated and the sessile benign tumors may closely resemble the



findings in cases of carcinoma. The sessile tumors at the pylorus may persist in showing such features. The pedunculated ones, however, frequently may change to an essentially normal picture with retreat of the tumor from the gastric outlet. Clinical symptoms usually follow a like pattern. Such findings have been emphasized by roentgenologists many times. It remains for the surgeon to supplement such reports with his clinical examination in order to more commonly make the diagnosis.

Strangulation may be a serious complication of these tumors, but since we have not observed it personally, we can add nothing to the present literature from this study.

Gastritis of varying degree has frequently been observed. It is probably more common than suspected and may account for many of the low grade symptoms in the relatively asymptomatic cases.

As previously stated, in 13.1 per cent of all the cases in which autopsy was performed there was malignant degeneration, polyps being present in 9 of the 10 cases. Thus of the 39 polyps autopsied 9 (23 per cent) showed malignant changes. In the last 16 operative and microscopically diagnosed benign gastric tumors, 3, or 19.2 per cent, had similar pathologic changes, limited exclusively to such mucous polyps. Such high figures are generally recognized and should not be overlooked in considering methods of treatment (table 7).

The following cases are briefly reported to illustrate some of the points considered significant in the clinical course of these benign tumors.

#### REPORT OF CASES

**CASE 1 (Fibromyoma).—**F. C., a 57 year old white man, was admitted on Feb. 2, 1935, with a ten year history of irregular epigastric pain, nausea and vomiting. Diet and the giving of alkalis had produced little relief. All symptoms had progressed in the last three years. He had lost weight but had never had bloody stools or vomitus. Except for loss of weight the physical examination showed little. Six months previously roentgen studies had shown annular constriction with defective filling of the prepyloric area with gastric retention. A diagnosis of carcinoma of the stomach and arrested pulmonary tuberculosis was made.

Operation was done on February 12. A walnut-sized, freely movable mass in the stomach on the lesser curvature just proximal to the pyloric ring was removed by gastric resection with posterior Polya anastomosis. Signs of consolidation of both lower lobes developed on the twenty-sixth postoperative day, and the patient died. Postmortem examination showed tuberculous pneumonia.

**Gross Pathologic Examination.**—There was a firm tumor mass just proximal to the pylorus on the lesser curvature of the stomach. There was some hypertrophy of the pylorus.

**Microscopic Examination.**—This tumor was made up of smooth muscle with a moderate amount of fibrous tissue throughout.

**Pathologic Diagnosis.**—The pathologic diagnosis was fibromyoma.

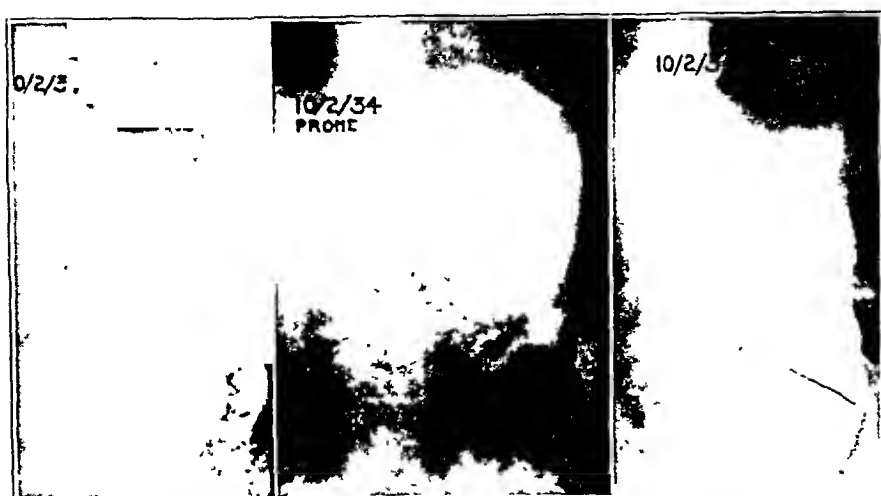


Fig. 1 (case 1).—Preoperative gastric roentgenograms of a dilated stomach with a prepyloric defect interpreted as malignant disease.



Fig. 2 (case 1).—Photomicrograph of a specimen described as fibromyoma.



Fig. 3 (case 2).—Preoperative gastric roentgenogram showing a circumscribed translucent area in the prepyloric region the size of a walnut which was interpreted as being a benign tumor.



Fig. 4 (case 2).—High power photomicrograph of a tumor excised locally from the pylorus and reported as a fibroleiomyoma.

This patient had a benign intramural tumor at the pylorus causing long-standing symptoms of obstruction. Gastric resection was unnecessarily carried out and may have contributed to the lighting-up of the old tuberculosis.

**CASE 2 (Fibroleiomyoma).**—J. D., a 50 year old white man, was admitted to the hospital Feb. 16, 1940. His illness began thirteen months previously with emesis of about 1½ cups (177 cc.) of bright red blood. Shortly thereafter he had tarry stools, became weak and spent nineteen days in the hospital. After that symptoms of nausea, vomiting and loss of weight steadily progressed with little relief from alkaline powders and diet. Two weeks before admission less severe hematemesis recurred. Physical examination showed a somewhat emaciated white man without other significant findings. All laboratory work fell within normal limits. Roentgenograms on February 19 showed a walnut-sized, translucent, circumscribed area in the prepyloric region of the stomach interpreted as a benign tumor.

Operation was done on February 21. A small intramural mass was locally excised. The patient made an uneventful recovery, being discharged on his twenty-third postoperative day.

**Gross Pathologic Examination.**—Macroscopic examination showed the specimen to consist of an irregularly shaped piece of tissue about 1.5 by 0.5 by 0.5 cm. Its surface was uneven, and it was white and firm.

**Microscopic Examination.**—On section there was seen much muscle and fibrous tissue which ran in all directions. There was a slight attempt at whorl formation. There was no evidence of infection or malignancy. No mucosa was seen, which would identify the tissue definitely.

**Pathologic Diagnosis.**—The pathologic diagnosis was fibroleiomyoma.

**Course.**—The patient remained well for about one year, when there was recurrence of symptoms due to a small gastric ulcer. This was not found either on the first roentgen examination or at operation (figs. 3 and 4).

This patient was exactly similar to the patient in case 1 except that in his case obstruction was complicated by hemorrhage.

**CASE 3 (Leiomyoma).**—E. E., a 58 year old white woman, was admitted to the hospital Sept. 21, 1937, with rather sudden onset of dizziness and fainting spells. Four days before she had vomited a large amount of blood. She had had tarry stools for three days. Except for irregular indigestion, the rest of the history was not pertinent. The patient was in mild shock. The pulse rate was 120. The blood pressure was 140 systolic and 60 diastolic. The red blood cell count was 1,600,000. The hemoglobin content was 30 per cent. The stools and the vomitus both gave positive reaction for blood. Roentgen examination on October 18 was reported as showing no gastric retention with request for reexamination, but roentgen examination on October 29 was reported to show a persistent defect in the antral region of the stomach suggestive of a neoplasm.

Operation was done on November 10. A firm pedunculated mass the size of a golf ball attached to the posterior wall along the greater curvature and prolapsed to the pylorus was excised by gastrotomy. The patient had an uneventful postoperative course. At the time of writing she had been followed for four years and is in good condition without symptoms. A check series of gastric roentgenograms done on December 15 showed a normal stomach and duodenum.

**Pathologic Diagnosis.**—The pathologic diagnosis was leiomyoma (figs. 5 to 11).

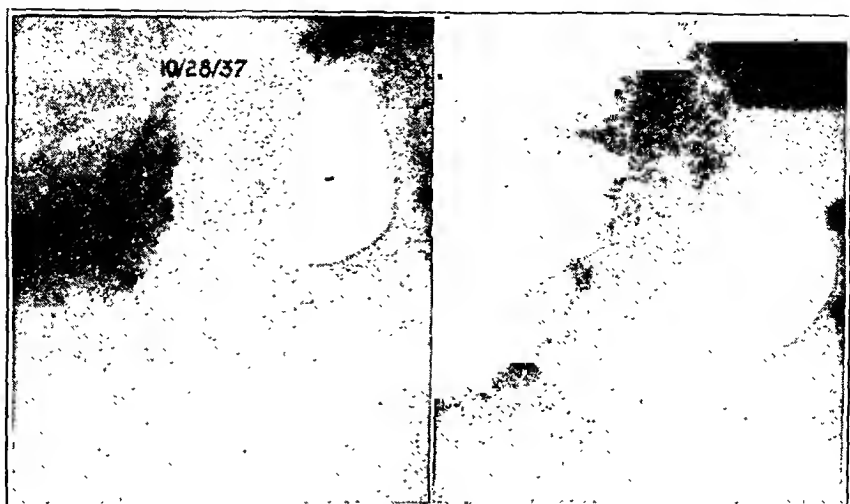


Fig. 5 (case 3).—Preoperative gastric roentgenograms showing a dilated stomach with retention and persistent antral defect suggestive of new growth. Roentgenograms taken ten days previously failed to show any such changes.

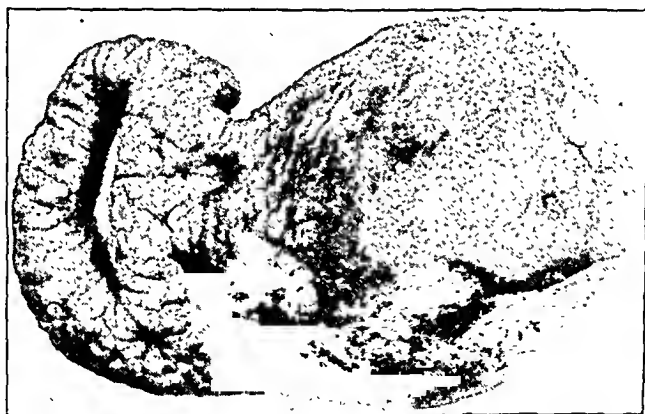


Fig. 6 (case 3).—View of a tumor excised locally from the greater curvature near the pylorus of the stomach.

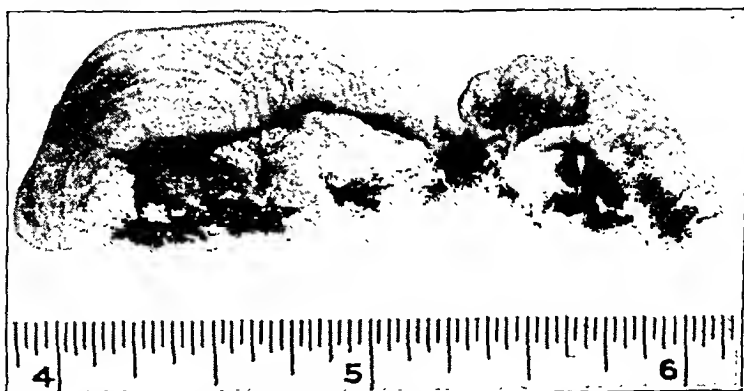


Fig. 7 (case 3).—View of the tumor in figure 6 showing ulceration.



Fig. 8 (case 3).—View of the tumor in figures 6 and 7 showing encapsulation.



Fig. 9 (case 3).—Low power photomicrograph of a specimen reported as leiomyoma.

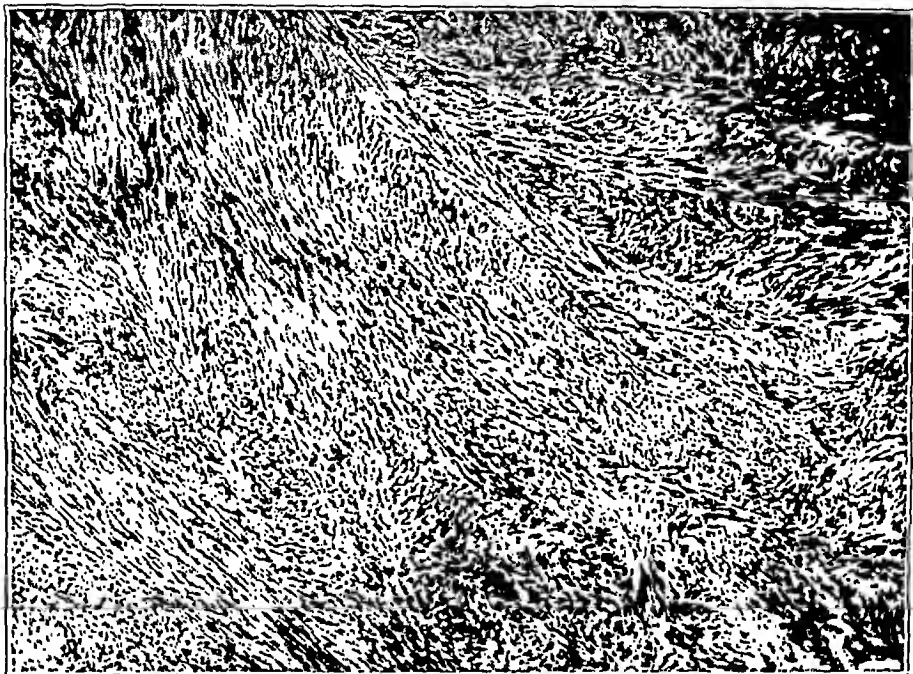


Fig. 10 (case 3).—High power photomicrograph of specimen shown in figure 9.

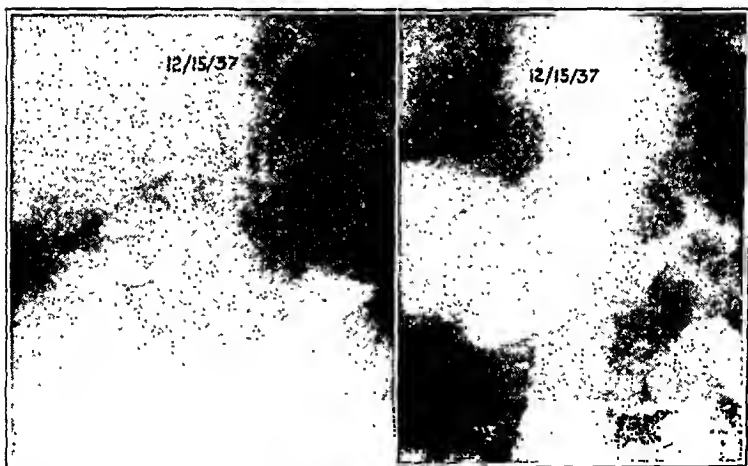


Fig. 11 (case 3).—Postoperative gastric roentgenograms showing an essentially normal picture.

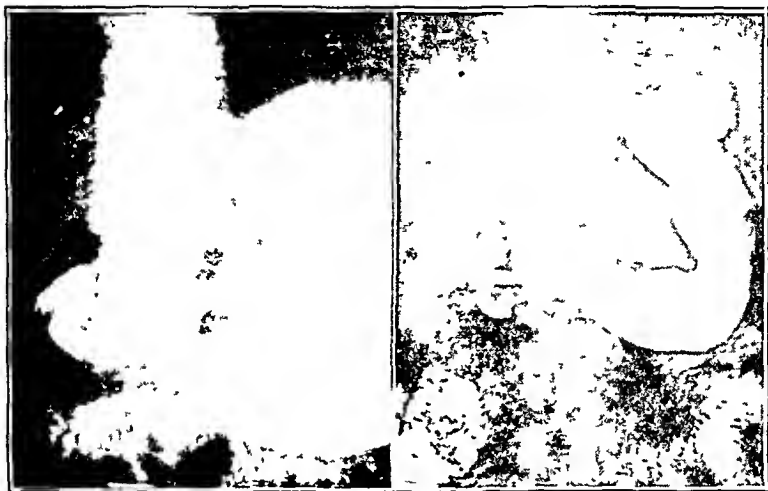


Fig. 12 (case 4).—Preoperative roentgenogram showing a persistent antral defect suggestive of a possibly benign neoplasm.

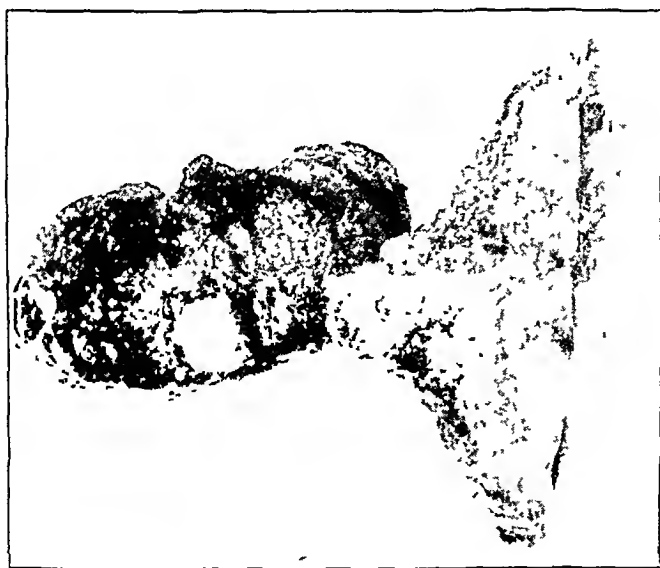


Fig. 13 (case 4).—Photograph of a gross specimen of a pedunculated tumor the size of a golf ball excised from the greater curvature of the stomach just above the pylorus.



This patient's first symptom was hemorrhage severe enough to force hospitalization for shock. Gastric roentgen studies done only ten days apart showed widely varying findings owing to the mobility of the tumor. This is not uncommon.

CASE 4 (Polypoid adenoma).—M. H., a 65 year old white woman, was admitted to the hospital Aug. 3, 1940, with difficulty in swallowing of approximately one year's duration. She had been known to have goiter for about seven years. The complaints which brought her into the hospital were marked weakness, dizziness and cardiac palpitation. She was an elderly woman who was extremely anemic. A large colloid goiter was present in the neck; other physical findings were essentially normal. On admission the hemoglobin content was 30 per cent; the red



Fig. 14 (case 4).—Low power photomicrograph of a specimen reported as polypoid adenoma.

blood cell count was 2,500,000. The stools gave a positive reaction for blood, and gastric analysis showed no free hydrochloric acid with a total of 50. The basal metabolic rate was + 28 per cent.

*Course.*—The patient was worked up to learn the cause of the anemia. On September 9 roentgen examination of the stomach showed a translucent area in the pyloric region of the stomach without any disturbance in the contour of the rest of the stomach. This was interpreted as a benign polyp. An episternal and substernal thyroid was also found on roentgen examination. The patient was given three blood transfusions; the hemoglobin content rose to 74 per cent and the red blood cell count, to 4,200,000.

Operation was done on September 12. A polypoid adenoma 2 by 1 cm. attached to the greater curvature just above the pylorus was locally excised. The patient had an uneventful postoperative recovery and was discharged on the

twentieth postoperative day. She returned a month later; at that time thyroidec-tomy was done. She was discharged on the fourteenth postoperative day. At the time of writing she has been followed for one year and is in excellent condition. Incidentally, gastric acidity has returned to normal levels.

*Gross Pathologic Examination.*—The specimen consisted of a pedunculated piece of tissue 2 by 1 cm. It was oval and hung from a stem attached to a base which was 2 by 2 by 1 cm. On section the base was observed to be white and the tumor part reddish brown.

*Microscopic Examination.*—The base consisted of mucosa and submucosa. The mucosa was typical gastric mucosa. A fibrous tissue stem extended out to the tumor. This stem contained blood vessels and occasional dilated acini lined with mucous cells. The mass itself consisted of dilated acini lined with mucous cells.



Fig. 15 (case 4).—High power photomicrograph of the specimen shown in figure 14.

There was considerable inflammatory cell invasion of the interacinous tissues, and edema was present.

*Pathologic Diagnosis.*—The pathologic diagnosis was benign gastric polyp (figs. 12 to 15).

CASE 5 (Adenomatous polyp, ulcerated).—T. G., a 51 year old white man, was admitted to the hospital Jan. 2, 1930, with a four months' complaint of increasing weakness with some nausea. There was no other significant history. The patient had anemia; the red blood cell count was 2,500,000; and the hemoglobin content was 35 per cent. In the course of work-up to learn the cause of the anemia, gastric roentgen examination was reported January 7 as follows: The barium sulfate on entering the duodenum surrounded the outer circumference with a central translucent area suggesting the presence of a polyp of the stomach or the duodenum.

Operation was done on February 28. A pedunculated tumor the size of an orange attached to the greater curvature  $2\frac{1}{2}$  inches (6.35 cm.) above the pylorus



Fig. 16 (case 5).—Preoperative roentgenogram showing barium sulfate surrounding a translucent area in the duodenum indicative of prolapse of the tumor through the pylorus.



Fig. 17 (case 5).—Photomicrograph of a specimen reported as adenomatous polyp.

was excised. This had prolapsed through the pylorus and was widely ulcerated. The patient was in poor condition at the time of operation and died on the third postoperative day of bronchopneumonia.

*Pathologic Diagnosis.*—The pathologic diagnosis was adenomatous polyp.

The finding of this adenomatous polyp was incidental to the diagnosis of the cause of severe anemia. The ulceration and prolapse through the pylorus without doubt accounted for the severity of symptoms (figs. 16 and 17).

CASE 6 (Adenomatous polyp with gastric ulcer).—E. K., a 53 year old white man, was admitted to the hospital Nov. 10, 1937, with a history of epigastric pain, nausea and vomiting of three months' duration and loss of 20 lb. (9.1 Kg.) in one year. The patient was emaciated. The red blood cell count was 3,900,000.

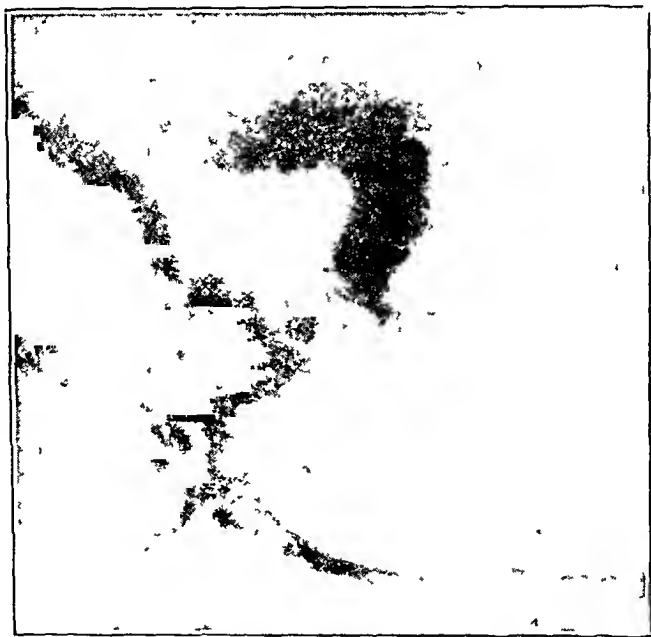


Fig. 18 (case 6).—Preoperative roentgenogram showing a pyloric defect with gastric retention interpreted as possible carcinoma.

The hemoglobin content was 80 per cent. The stools gave a 3 plus reaction for blood. Roentgen examination on November 12 was reported to show gastric retention with defect at the pylorus. Preoperatively a diagnosis of carcinoma was made.

On November 30 subtotal gastric resection with posterior Polya anastomosis was done because the tumor of the stomach was adherent to the liver and thought to be malignant. The patient made an uneventful recovery after operation.

*Gross Pathologic Examination.*—A gastric ulcer on the lesser curvature with four polyps the size of walnuts on the greater curvature at the pylorus was found by macroscopic examination.

*Microscopic Examination.*—The microscopic examination was reported to show an adenomatous polyp of the stomach with a gastric ulcer of the lesser curvature.

This patient had a benign adenomatous polyp on the greater curvature and a gastric ulcer on the lesser curvature (figs. 18 and 19).

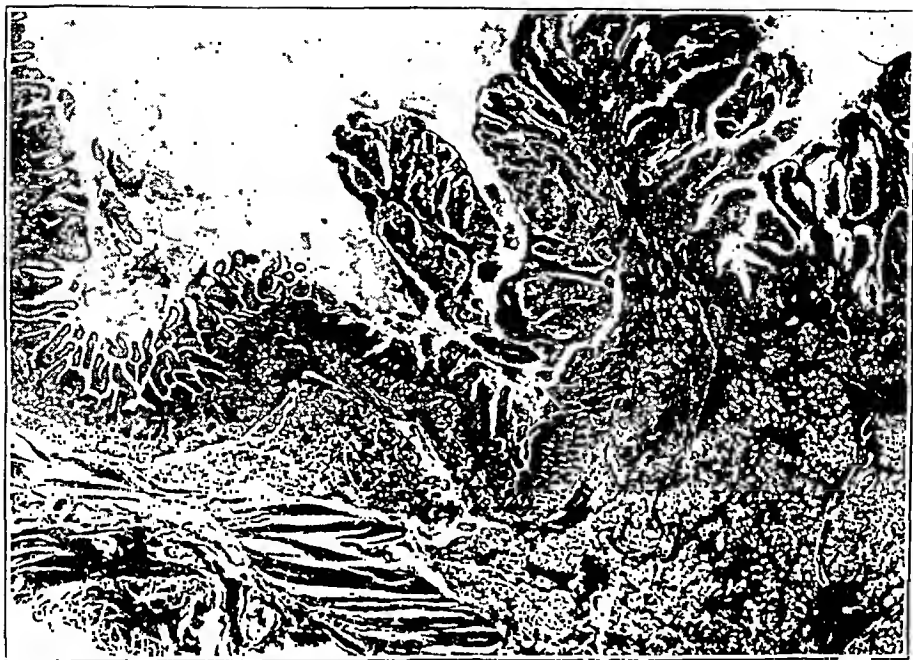


Fig. 19 (case 6).—Photomicrograph of an adenomatous polyp of the greater curvature of the stomach removed by gastric resection. It was associated with a gastric ulcer of the lesser curvature.

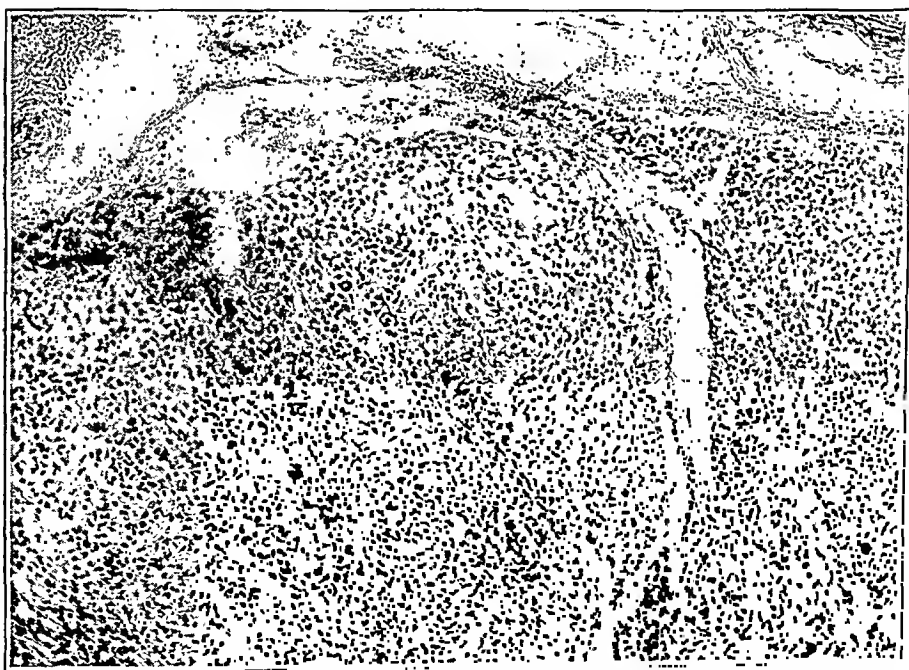


Fig. 20 (case 7).—Photomicrograph of a rare type of benign gastric tumor. The pathologists reported this to be hemangioendothelioma.

CASE 7 (Hemangioendothelioma).—P. B., a 56 year old white man, was admitted to the hospital Sept. 4, 1929, with a twenty year history of indigestion and recent onset of weakness, nausea, vomiting and loss of weight. He was chronically ill, emaciated and had a red blood cell count of 2,200,000 and a hemoglobin content of 22 per cent. Roentgen examination on September 10 was reported to show a well defined pyloric lesion with loss of rugose markings. A benign tumor was suspected because of the perfect regularity of the greater and lesser curvatures. A diagnosis of possible benign pyloric tumor was made.

Operation was done on September 17. By gastrotomy a multilobular well encapsulated tumor at the pylorus was removed. It was firm with some semi-cystic areas and was readily shelled out from beneath the mucosa, which was



Fig. 21 (case 8).—Photomicrograph of a rather rare type of benign gastric tumor. This was reported to be cellular fibroma.

not ulcerated. The patient made an uneventful recovery and was followed for four years; when last seen, he was perfectly well.

*Pathologic Report.*—Since this was a rather rare type of tumor, we shall give the complete pathologic report: The mass showed thin-walled small blood vessels embedded in richly cellular tissue with the cells of indefinite histologic nature. The preponderant cell was small and sharply outlined and had a sharply limited membrane. The cytoplasm stained lightly. The nucleus was small, oval and poorly chromatic. There were small thin-walled vessels; single and in groups, lined with endothelium.

*Pathologic Diagnosis.*—The pathologic diagnosis was hemangioendothelioma (fig. 20).

CASE 8 (Cellular fibroma[?]).—C. B., a 60 year old white woman, was admitted to the hospital May 7, 1925, with six weeks' history of epigastric pain, nausea

and vomiting with slight initial jaundice and a loss of 40 lb. (18.1 Kg.). She was chronically ill and slightly icteric and had a tender abdomen and an enlarged liver. Stools gave a positive reaction for blood. The red blood cell count was 1,600,000 and the hemoglobin content 28 per cent. Seven days after admission the patient vomited 14 oz. (4.14 cc.) of material resembling coffee grounds which gave a positive reaction for blood. Six days later increasing icterus was noted, and the stools became clay colored. Roentgen examination showed a gastric neoplasm at the pylorus. Preoperatively a diagnosis of obstruction of the common duct was made, probably from an extension of pyloric carcinoma.

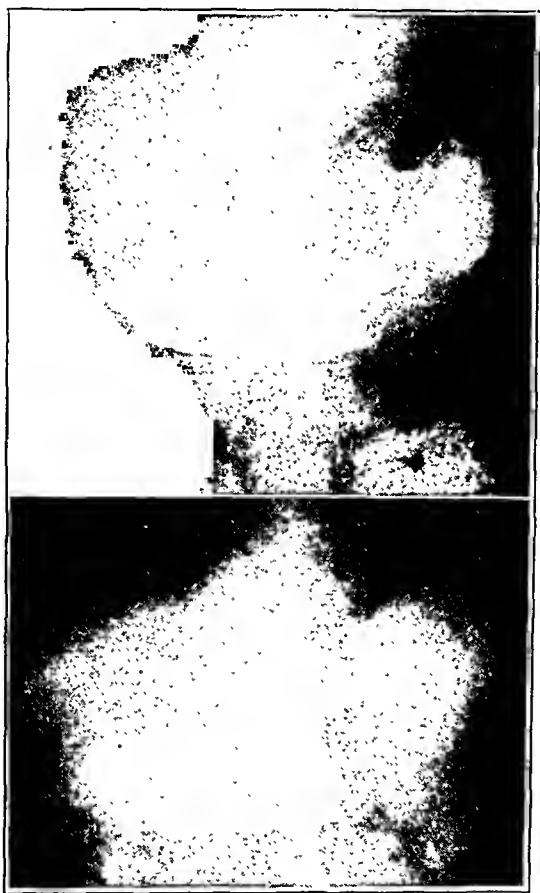


Fig. 22 (case 9).—Preoperative roentgenogram showing a well outlined tumor in the lumen of the stomach with a crater at the apex.

Operation was done on May 25. A common duct stone was removed from the ampulla by duodenotomy with drainage of the common duct. A large sessile ulcerated mass at the lesser curvature on the posterior wall near the pylorus was easily removed by gastrotomy. The patient made an uneventful recovery and at the time of writing has been followed for over ten years, being perfectly well at the age of 75 (fig. 21).

*Pathologic Report.*—The tumor was somewhat lobulated and exceedingly soft and friable. It appeared to be vascular. The tumor was entirely submucous and apparently did not involve the muscularis.

*Microscopic Examination.*—Sections taken from different areas showed dissimilar histologic pictures. In parts the tumor showed a cellular mass of long spindle connective tissue cells of adult character. Other sections suggested an epithelial origin, but they did not resemble cells derived from glandular epithelium. The general impression was that the tumor was a cellular fibroma.



Fig. 23 (case 9).—Gross specimen showing an ulcer at the apex.

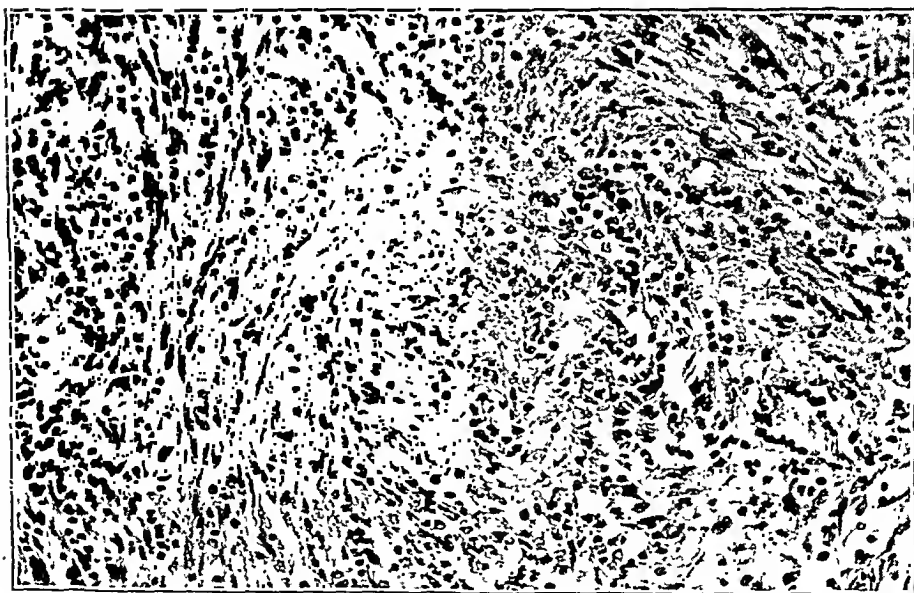


Fig. 24 (case 9).—Photomicrograph of a specimen reported by the pathologist to be leiomyoma of the stomach with chronic ulcer.

CASE 9 (Leiomyoma).—G. O'B., a 57 year old white man, was admitted to the New York Hospital on Dec. 3, 1941. Four months previous to admission, while at work, he suddenly fainted and was told that he had vomited a large amount of blood. He was admitted to another hospital as an emergency patient, and a diagnosis of bleeding duodenal ulcer was made. After receiving several blood transfusions and dietary treatment, he was discharged from the hospital to



have roentgen studies of the stomach made in about two weeks. At this time the gastrointestinal roentgen series did not show a duodenal ulcer; neither was a positive diagnosis of benign tumor made. About two weeks before admission to the New York Hospital another gastrointestinal series was reported as showing a regular filling defect in the distal third of the stomach without obstruction. A diagnosis of benign tumor of the stomach with ulceration of the tumor, probably leiomyoma, was made.

At operation on December 6 a tumor the size of a golf ball attached by a broad pedicle to the posterior wall of the stomach along the greater curvature in the distal third was removed through gastrotomy. The patient made an uneventful recovery and was discharged from the hospital on December 20.

*Gross Pathologic Examination.*—The tumor was the size of a golf ball and had a punched-out ulcer 1.5 cm. in diameter at its apex. The center of the tumor was moderately soft, secondary to some degeneration.

*Microscopic Examination.*—Microscopic examination showed leiomyoma of the stomach with a chronic ulcer with some hypertrophy and degeneration of interlacing bundles of smooth muscle.

This is another instance of the onset of symptoms with severe hemorrhage in a previously well person.

#### SUMMARY AND CONCLUSIONS

In 108 cases of benign gastric tumor 76 of the lesions were found at autopsy and 32 at operation. For various reasons the vast majority of these were not correctly diagnosed previous to death or operation. Many remained practically asymptomatic without apparent detriment to the person. Others, however, produced alarming symptoms, the complexity of which often led to error. Practically all of the mistakes can be traced to confusion with either gastric carcinoma or bleeding peptic ulcer.

With the benign tumor pyloric obstruction and hemorrhage are the common complaints requiring treatment and combine with the occasional close resemblance to carcinoma or peptic ulcer on roentgen examination to account for most of the errors. Although these similarities have been recognized, some points of value in differential diagnosis have been singled out and described as the experience of this study.

The hazards of severe hemorrhage and malignant degeneration constitute valid indications for surgical treatment of all benign gastric tumors. Local excision usually suffices except for the sessile adenomatous polyps at the pylorus. Gastric resection is probably indicated in this subgroup of tumors in view of the high incidence of malignant degeneration.

# CYSTS OF THE PANCREAS

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In spite of the infrequent occurrence of cystic disease of the pancreas, the condition not only is of interest from the pathologic point of view but also is of practical importance. Cystic disease of the pancreas has long been recognized as a clinical entity. Its symptoms have been adequately described; its causation has been surmised, and certain of its pathologic aspects have been studied.

The basis of this report is a study of 17 cases of cysts of the pancreas. This includes all the cases collected from the records of Jewish Hospital. In 14 cases operation was performed. In some cases it was difficult for the operating surgeon to identify the cyst in relation to the surrounding structures and to determine whether it was a true pancreatic cyst or a so-called pseudocyst. In only 1 case was the tumor malignant.

## AGE AND SEX INCIDENCE

Pancreatic cyst may occur at any age but is most often seen in persons about middle life. Telling and Dobson<sup>1</sup> described a case in which the patient was an 11 month old child. The ages of the patients in this series ranged from 21 to 76 years, averaging 45.4. The age period of greatest frequency was from 21 to 49 years. There were 14 female and 3 male patients, showing a preponderance of the disease among female patients.

## PATHOGENESIS

Owing to lack of knowledge concerning the pathogenesis of the various types of pancreatic tumor, classifications are necessarily at variance. Robson and Moynihan<sup>2</sup> grouped these neoplasms as retention cyst, proliferative cyst (including cystic adenoma and cystic epithelioma), hydatid cyst, congenital cystic disease, hemorrhagic cyst and pseudo-

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From the Departments of Surgery and Pathology, Jewish Hospital.

1. Telling, W. H., and Dobson, J. F.: Pancreatic Cyst in an Infant, *Brit. J. Child. Dis.* 6:202, 1909.

2. Robson, A. W. M., and Moynihan, B. G. A.: *Diseases of the Pancreas and Their Surgical Treatment*, Philadelphia, W. B. Saunders Company, 1903, p. 188.

cyst. Judd's<sup>3</sup> inclusion of dermoid cyst seemed to complete the list. Analysis of the series on which this study is based, however, has disclosed another form of pancreatic cyst which to our knowledge has not been heretofore described in the literature. As will be seen later, this tumor originates from Brunner's glands included in the pancreas because of some fault in embryonic development.

An outline of the different forms of pancreatic cyst described in this paper is given in table 1.

It is the consensus that pseudocyst is more frequent of occurrence than the other forms of cystic tumor of the pancreas; this also holds true in this series. The cyst may occur in any portion of the organ although it is most prevalent in the tail.

The origin of pancreatic cyst has been a matter of conjecture since it was first described. The pathologic description of the growth encountered in the reported cases makes one suspect that in the majority of instances the lesion is the result of some form of trauma to the

TABLE 1.—*Types of Pancreatic Cyst Encountered in This Study*

Type of Cyst	Cases
Pseudocyst .....	11
Cystadenoma .....	2
Retention cyst .....	2
Inclusion cyst (Brunner's gland).....	1
Cyst with carcinomatous changes.....	1

pancreas. This is particularly significant with regard to pseudocyst. Körte<sup>4</sup> proposed the term "pseudocyst" for a fluid tumor found in more or less close proximity to the pancreas but not originating in the substance of the gland, the most frequent examples being those of effusion into the lesser sac of peritoneum as a result of injury to the pancreas. Lloyd<sup>5</sup> was among the first to point out that the majority of pseudocysts following abdominal injury were not true retention cysts of the pancreas. He reported 2 cases, both occurring after abdominal injury—one three weeks and another three months after trauma. He expressed the opinion that both were associated with injury to the pancreas, probably by pressure against the first lumbar vertebra. Willis and Budd<sup>6</sup> restricted the term "pseudocyst" to a cyst resulting from trauma.

3. Judd, E. S.: Cysts of the Pancreas, *Minnesota Med.* 4:75, 1921.

4. Körte, W.: Zur Behandlung der Pankreaszysten und Pseudozysten, *Deutsche med. Wchnschr.* 37:536, 1911.

5. Lloyd, J.: Injury to the Pancreas: A Cause of Effusion into the Lesser Peritoneal Cavity, *Brit. M. J.* 2:1051, 1892.

6. Willis, A. M., and Budd, S. W.: Pancreatic Cysts, with Report of a Case, *Surg., Gynec. & Obst.* 20:688, 1915.

Of 117 cases collected from the literature by Körte in 1911 there was a definite history of abdominal injury in 33. Among 41 cases collected by Judd in the records of the Mayo Clinic, trauma seemed to be a causative factor in 1 case only, the cyst occurring two months after the injury.

Experimental evidence also lends support to the view that trauma is an important causative agent in the production of pseudocyst of the pancreas. Lazarus<sup>7</sup> was able to produce such a cyst by crushing the pancreas of a dog. A hematoma first formed, which later became an encapsulated cyst and contained 100 cc. of milky fluid. These clinical facts together with the experimental evidence of Lazarus point to trauma as a factor in the production of pseudocyst of the pancreas.

While this conception of the causation of pseudocyst of the pancreas does not account for all cystic processes of this sort under all conditions, it offers a reasonable explanation of the majority of them and is in accord with the personal experience of many victims of the disease. Sufficient evidence has accumulated, however, which points to other agents besides trauma as causative factors. Thus it is well known that after certain inflammatory conditions of the pancreas or the gallbladder pseudocyst may develop in the pancreas. It is also of importance to note that in many instances no cause whatsoever could be discovered to account for the formation of the cyst. In none of our patients was a history of trauma elicited, nor was any coexisting condition found which could have been responsible for the hemorrhage in the pancreas. In the first 11 of the following cases the growth was a pseudocyst.

#### REPORT OF CASES

CASE 1.—C. G., a woman aged 56, was admitted to the hospital with generalized abdominal pains of several years' duration. The cramps were said to be relieved by catharsis and enemas. During the last six months before admission the cramps became intensified, and the abdomen increased in size. She had lost considerable weight and grown weaker, and swelling of the lower extremities developed. Physical examination at the time of admission revealed an emaciated woman. The abdomen was large and tense and was the seat of a tender mass which extended from the pelvis to about 3 fingerbreadths above the umbilicus. There was evidence also of free fluid in the peritoneal cavity. A diagnosis of retroperitoneal tumor was made, and the abdomen was opened through a median lower incision. The abdominal cavity contained a large amount of free straw-colored fluid and a large retroperitoneal cyst the anterior surface of which was adherent to the parietal peritoneum. The cyst appeared to arise in the region

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7. Lazarus, P.: Beitrag zur Pathologie und Therapie der Pankreaserkrankungen mit besonderer Berücksichtigung der Zysten und Steine, Ztschr. f. klin. Med. 51:95 and 203, 1904.

of the body of the pancreas; it was aspirated, and a thick gelatinous brown fluid was obtained. The cyst was drained, and the patient made an uneventful recovery. Chemical examination of the aspirated fluid showed mucus, diastase and trypsin.

CASE 2.—E. F., a 35 year old housewife, was admitted to the hospital with persistent vomiting of eighteen hours' duration. During a routine examination two months before, her physician had discovered a lump in the left upper quadrant of the abdomen. She lost considerable weight and was subject to attacks of headaches and dizziness. Cholecystectomy and appendectomy were performed three years previously. She was well developed and well nourished but apparently extremely ill; she retched constantly. In the left hypochondrium there was a round, firm, ballotable and nontender mass about the size of a grapefruit. Roentgen examination showed displacement of the stomach upward and to the right by a large extrinsic soft tumor mass which also encroached on the greater curvature. Examinations of the blood and the urine revealed no abnormalities. A diagnosis of omental or pancreatic cyst was made. At operation a large blue cystic tumor was observed occupying the lesser sac. It displaced the ascending layer of the transverse mesocolon upward. The tumor was approached through the gastrocolic omentum; the wall was incised, and several quarts of blood-stained fluid together with coagulated and necrotic debris was evacuated. The cystic wall was marsupialized to the anterior abdominal wall, and three cigaret drains were left in situ. A small portion of the cyst was removed for examination. The wound continued to drain for two weeks; during this time a clear fluid was discharged in decreasing amounts. The patient made complete recovery in six weeks.

Biopsy showed part of the surface wall to be covered with cylindric epithelium. The rest of the wall consisted of dense layers of granulation tissue infiltrated in places with round cells, large mononuclear cells and some polymorphonuclear leukocytes. Another portion of the surface was thrown into coarse folds, and in the deeper layers were spaces lined by low cuboid cells as well as tubular and duct structures lined by cylindric cells.

CASE 3.—S. H., a 47 year old woman, was admitted to the hospital with the complaint of severe abdominal pain, distention and vomiting of three weeks' duration. She complained also of continuous cutting pains in the lumbar region; she had lost considerable weight.

On examination the patient was observed to be well developed and well nourished and apparently not acutely ill. There was tenderness over the hypogastrium and the right hypochondrium but more particularly in the region of the gallbladder. No masses could be palpated in the abdomen. The laboratory findings included: blood sugar, urea, creatinine and cholesterol; these were normal. A Wassermann test of the blood had a negative result; the blood count was normal; the urine was normal. Roentgen examination of the stomach revealed retention of barium sulfate after a six hour period. The normal acute angle at the junction of the first and second portions of the duodenum was changed to almost a semicircular form, indicating separation of the first and second duodenal segments by enlargement of the head of the pancreas. A diagnosis of pancreatic tumor was made, and at operation a large mass the size of a fetal head could be felt extending from the ensiform process to the umbilicus. The stomach was displaced to the left and downward, and the gastroepiploic omentum was pushed forward by a mass immediately under it. Aspiration of this mass yielded more

than a liter of light gray fluid mixed with blood and globules of oil. The gallbladder was markedly distended. Drainage of the cyst was effected through marsupialization to the anterior abdominal wall; the gallbladder also was drained. Chemical analysis of the aspirated fluid revealed an alkaline reaction, a specific gravity of 1.014, the presence of cholesterol, trypsin and albumin but no bile. Microscopic examination of the fluid showed debris, cholesterol crystals, fatty acids, fat globules and desquamated epithelium. Culture of the fluid was sterile.

The postoperative course was complicated by excoriation of the skin. This was treated with Beck's paste and zinc oxide. The patient was discharged forty-five days later well improved.

CASE 4.—F. F., a 21 year old woman, was admitted to the hospital because of rapid enlargement of the abdomen during the previous six months. This was associated with increasing constipation, dyspnea and frequency of urination. The appendix had been removed six years previously. On examination the patient was observed to be well developed and well nourished. The abdomen showed a huge tumor mass extending from the symphysis pubis to 6 fingerbreadths above the umbilicus and to both flanks. The mass was firm and dull to percussion. A diagnosis of ovarian cyst was made.

At operation a cyst about the size of a large melon could be felt in the retroperitoneal tissues in the upper portion of the abdomen, probably arising from the pancreas. Projecting upward from this mass, another smaller cyst the size of an orange could be felt. Aspiration of the mass yielded a considerable amount of dark hemorrhagic liquid material. The cyst was incised; its contents were evacuated, and the wall was marsupialized. Three drains were left in situ. The patient made an uneventful recovery.

Examination of the aspirated fluid revealed the following: Culture was sterile. There was amylase but no trypsin or bile. Cytologic examination revealed degenerated polymorphonuclear leukocytes and lymphocytes.

CASE 5.—L. D., a 23 year old woman, was admitted to the hospital with the complaint of epigastric distress and constipation of six days' duration. Three days after the onset of her illness the pain radiated to the right lower quadrant of the abdomen and became sticky in character. When examined, the abdomen was soft and nontender, and no masses were palpable. A diagnosis of chronic appendicitis was made. At operation a retroperitoneal cyst the size of a plum was found in the region of the pancreas and was excised. The appendix also was removed.

Grossly, the excised specimen consisted of a cystic mass 3.5 cm. in diameter. The external surface was pearly white, smooth and glistening; the internal surface was smooth. The contents of the cyst consisted of yellow-gray mucoid material mixed with some necrotic debris. Chemical examination of this fluid revealed the presence of amylase. Microscopic examination of the cyst showed a portion of the wall surface lined by low cuboid cells; other areas were completely denuded of cell covering. The rest of the cyst wall consisted of dense layers of fibrous connective tissue in which were scattered a moderate number of lymphocytes and occasional small hemorrhages.

CASE 6.—J. G., a 31 year old woman, was admitted to the hospital with the complaint of pain in the left upper quadrant of the abdomen. Eight months previously she had been seized with an attack of pain in the left upper quadrant,

nausea, vomiting and diarrhea. She was confined to bed for ten days and felt much improved. Two months later the pain recurred with flatulence and distention. Since then she had been subject to repeated attacks of abdominal pain which came at intervals of two to four weeks. Two weeks before admission she had a sharp attack of pain in the left upper quadrant; this radiated to the left shoulder and the left side of the neck and was aggravated by deep breathing.

On examination the patient did not appear acutely ill. The abdomen presented an irregular nontender firm mass in the left upper quadrant, which moved freely with respiration. Roentgen examination of the chest and the gastrointestinal tract revealed no abnormalities. A diagnosis of pancreatic cyst was made, and the abdomen was opened through a left subcostal incision. A large cystic tumor about the size of a grapefruit was found in the tail of the pancreas. It extended upward under the diaphragm and downward posterior to the stomach and the spleen. Eight hundred cubic centimeters of old fluid blood was aspirated and found to contain amylase. Microscopic examination of a portion of the cyst wall showed dense layers of fibrous and hyalinized connective tissue enclosing numerous thin-walled blood vessels, lymphocytes and small areas of hemorrhage. The surface was denuded of epithelium.

CASE 7.—F. K., a 41 year old woman, was admitted to the hospital with sticking pains and a mass felt in the left upper quadrant of the abdomen. These complaints had been present for six months. The tumor began to grow at an extraordinarily rapid rate, and at the end of six months it filled the upper part of the abdomen.

On examination the patient was observed to be well developed and well nourished and restless. The abdomen was the seat of a huge tumor mass which occupied its entire left side. The mass felt partly semisolid and partly cystic.

Roentgen examination revealed a tremendous soft tissue mass occupying almost the entire left side of the abdomen, extending well below the crest of the ilium and reaching across the right side of the midline. A clysma of barium sulfate showed deviation of the transverse colon to the splenic flexure by a large mass in the left upper quadrant of the abdomen. A film taken in the lateral projection showed that this mass pushed the bowel anteriorly. Roentgen examination of the upper part of the gastrointestinal tract showed the stomach displaced anteriorly. These findings indicated that the mass probably originated in the region of the pancreas.

The laboratory findings were as follows: The icteric index was 5.8. The blood sugar content was 87 mg. per hundred cubic centimeters. The blood urea content was 10.2 mg. per hundred cubic centimeters. Cutaneous tests for ecchino-coccic cyst gave negative results.

A diagnosis of retroperitoneal sarcoma was made, although the possibility of a pancreatic cyst was entertained. At operation a tumor was felt retroperitoneally; this suggested cyst of the pancreas. The tumor extended far down into the pelvis but had no pelvic connections. It soon became evident that this was a retroperitoneal cyst which had developed downward and forward. Aspiration of this mass yielded a dark brown hemorrhagic fluid; approximately 5 liters of this was aspirated from this cystlike mass. Drainage was instituted at the site of aspiration, and the cyst wall was marsupialized after a small piece was removed for pathologic examination. The patient made an uneventful recovery.

Chemical examination of the aspirated fluid showed that the pancreatic enzymes were present; there was no bile. The fluid was sterile on culture. Biopsy showed the cyst wall to be composed of loose fibrous connective tissue. The surface was denuded of epithelium.

CASE 8.—G. G., a 49 year old woman, was admitted to the hospital with the complaint of intermittent attacks of pain in the left upper quadrant of the abdomen of five months' duration. The pain was said to arise in the left costovertebral area and radiate along the costal margin to the left upper quadrant. It recurred at intervals of two to three weeks, lasted a week and then subsided. She complained also of constipation and of the loss of 10 pounds (4.5 Kg.) since the onset of the illness.

On examination the patient appeared well developed and well nourished and not acutely ill. A large ballotable mass was present in the left upper quadrant of the abdomen. It extended from about 2 fingerbreadths beyond the midline to the right and along the left costal margin; it moved freely with respiration. Examinations of the blood and the urine revealed no abnormalities. A diagnosis of cyst of the pancreas was made.



Fig. 1.—Photograph showing gross appearance of pseudocyst of the pancreas. The surface is partly smooth and partly roughened by fibrous tags.

At operation a left subcostal incision was made, and a large cyst about 20 cm. in diameter was noted in the tail of the pancreas. It contained about 800 cc. of turbid hemorrhagic fluid. The entire cyst was excised. The splenic artery had to be ligated to facilitate removal of the cyst, and consequently the spleen also was removed. Chemical examination of the aspirated fluid revealed the presence of lipase and amylase; there was no bile.

Grossly, the tumor consisted of a thick-walled, opaque and oval-shaped mass 12 cm. in diameter. The external surface was pink-gray, partly smooth and glistening and partly roughened by fibrous tags. The wall measured up to 0.2 cm. in thickness. The inner lining of the cyst was smooth, glistening and trabeculated (fig 1).



Microscopically, the cyst wall consisted of dense layers of fibrous and hyalinized connective tissue. The inner surface was partly covered by a single layer of low cuboid epithelium (fig. 2).

The association of acute and chronic pancreatitis with the formation of these cysts is well established, and, in turn, the relation between infection in the gallbladder and the bile ducts as a causative factor, direct as to pancreatitis and indirect as regards cyst formation, must be taken into account. Analysis of our group of cases shows a definite relation between the development of acute pancreatitis and cholecystitis and

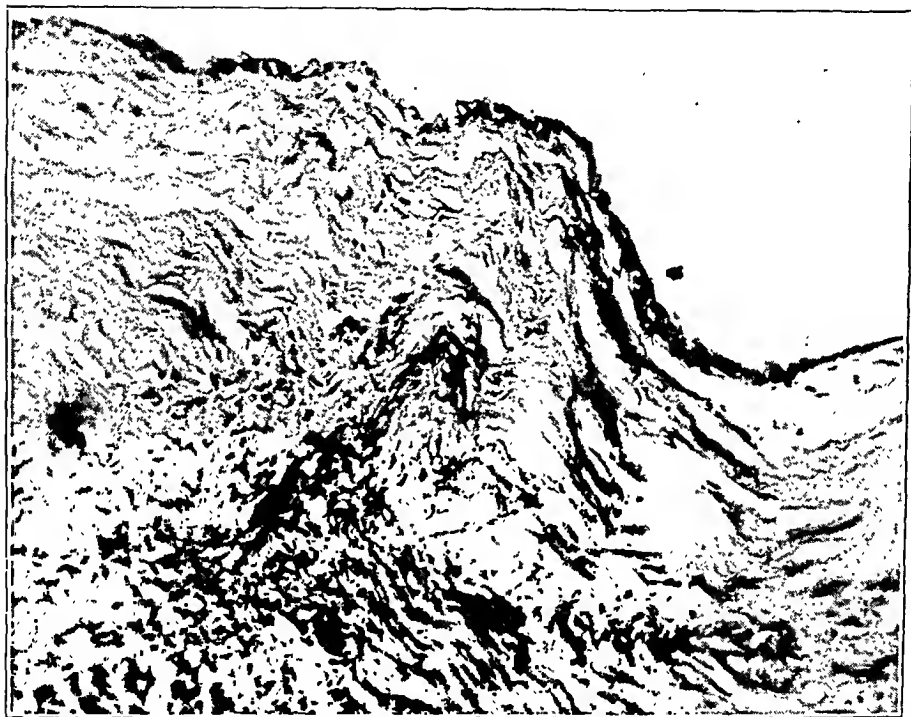


Fig. 2.—Photomicrograph showing the wall of the pseudocyst shown in figure 1. The inner surface is lined by a single layer of low cuboid epithelium. The rest of the wall is made up of dense layers of fibrous and hyalinized connective tissue.

the formation of some of these cysts. In 1 case pseudocyst of the pancreas was preceded by an attack of acute pancreatitis, and in 2 others it was preceded by attacks of acute cholecystitis.

CASE 9.—S. R., a 23 year old woman, was admitted to the hospital with the complaint of a sense of fulness and discomfort in the epigastrium of three months' duration. The pain radiated to the back and lasted several hours. For the last three weeks before admission the pain became more severe in character. On examination there was deep tenderness in the right hypochondrium and marked

spasm of the rectus muscles. A diagnosis of acute pancreatitis was made, and at operation a large quantity of serosanguineous fluid was found in the peritoneal cavity; there was evidence also of fat necrosis. After drainage was instituted, the abdomen was closed. The patient made a complete recovery and was discharged from the hospital three weeks later.

She returned after three months because of enlargement of the abdomen. Abdominal examination revealed a small tumor in the right upper quadrant; this was freely movable and was cystic in consistency. At operation a small cyst was observed in the region of the tail of the pancreas. The cyst was aspirated, and 45 cc. of sanguineous fluid was removed. The patient made an uneventful recovery. Chemical analysis was made of the aspirated fluid. The specific gravity was 1.025. The fluid gave an alkaline reaction. It contained no bile. Amylase was present, but there was no trypsin. The fluid gave a positive reaction to the guaiac test for blood.

CASE 10.—H. W., a 48 year old woman, was admitted to the medical service with the complaint of headaches, nausea, vomiting and pain in the back radiating to the epigastrium of ten years' duration. During the past eighteen months sharp stabbing pain had developed in the right costovertebral area and radiated to the front of the abdomen. This was followed by nausea and vomiting. The attacks usually occurred in the early hours of the morning and required the administration of morphine sulfate for relief. The attacks were most prone to occur after the patient had partaken of a fatty meal.

On examination the patient was observed to be well developed, rather obese and not acutely ill. The abdomen presented a tender area just to the right and above the umbilicus. A diagnosis of nephrolithiasis was made. While the patient was in the hospital, an acute attack of pain in the back which radiated to the right upper quadrant developed. Icterus soon developed, and bile appeared in the urine. The patient was transferred to the surgical service, and at operation an acutely inflamed gallbladder was found and removed. Her postoperative course was complicated by increasing jaundice, rise in temperature and severe pain in the left upper quadrant of the abdomen and in the back. On the sixteenth postoperative day the temperature rose to 103 F.; the abdomen became distended; there was fulness in the left flank, and large quantities of bile escaped through the wound. Roentgen examination revealed a large homogeneous opacity with well defined margins suggestive of a cystic mass in the left upper quadrant of the abdomen. Intravenous pyelographic examination revealed nothing unusual. The patient was operated on again six weeks after removal of the gallbladder, and a large retroperitoneal cystic mass about the size of a football was found in the region of the pancreas. The cyst was incised, and approximately 4 quarts (3.8 liters) of green fluid was evacuated. It was then marsupialized, and two drains were left in situ. The patient made an uneventful recovery.

Pathologic examination of the cyst wall showed it to consist of lobules of adipose tissue and dense bands of hyalinized connective tissue enclosing numerous newly formed capillaries, round cells, polymorphonuclear leukocytes and eosinophils. Chemical analysis of the aspirated fluid showed a small amount of bile, amylase and lipase. Culture of the fluid was sterile.

CASE 11.—L. B., a 72 year old woman, was admitted to the hospital with a history of progressive jaundice of six weeks' duration and clay-colored stools,

itchiness and general abdominal pain of four weeks' duration. She had lost some weight. Eleven years previously posterior gastroenterostomy had been performed for duodenal ulcer.

On admission the patient was observed to be well developed, obese and icteric. A moderately tender mass was present in the right upper quadrant of the abdomen. The icteric index was 50; urea was 73; total cholesterol was 213 mg. per hundred cubic centimeters, and free cholesterol was 63 per cent. Phosphatase was 10.6, and sugar was 83.

A diagnosis of carcinoma of the pancreas was made, and at operation there was found an acutely inflamed thick-walled gallbladder with two stones lying free in its cavity and another stone impacted in the cystic duct. In addition, the head of the pancreas was the seat of a cyst about the size of an orange. The cyst was incised; its contents were aspirated, and the wall was marsupialized. The gallbladder was drained. After operation the jaundice subsided, and the patient was discharged on the fourteenth postoperative day well improved.

Cystadenoma of the pancreas is not a common finding; it occurred in 2 cases in our series. The tumor is usually small and well circumscribed and arises from the parenchyma of the pancreas. Cystadenoma is therefore a true pancreatic tumor and is distinguished from retention cyst by the abundant growth of epithelial papillae.

CASE 12.—E. S., a 28 year old man, was admitted to the hospital because of blood in the stools and sharp pain in the lower part of the abdomen of two days' duration. He was known to have suffered from peptic ulcer for ten years, and he had been receiving a Sippy diet for the last four years before admission.

On examination the abdomen presented nothing unusual. The stools gave a strong positive reaction for blood. A diagnosis of bleeding duodenal ulcer was made. For this he was operated on through an upper right rectus incision. As the peritoneal cavity was opened, a small mass 4 inches (10.2 cm.) in diameter was found in the head of the pancreas. A small ulcer also was found on the anterior surface of the first portion of the duodenum. The cyst was excised, and the abdomen was closed after drainage was instituted at the site of excision.

Grossly, the specimen consisted of a multiloculated cyst 6 by 3 by 0.8 cm. The external surface was partly smooth and glistening and partly rough and irregular in outline. On section it was observed to contain a milky fluid. Microscopically, the cyst wall itself was thin, being made up of loose fibrous tissue and smooth muscle bundles, lined on its inner surface by a single layer of somewhat flattened epithelial cells. The connective tissue was infiltrated in places with round cells.

CASE 13.—S. L., a 45 year old woman, was admitted to the hospital because of epigastric distress of five months' duration. On examination the patient was seen to be well developed and well nourished and not acutely ill. The abdomen presented a small mass in the upper quadrant just to the left of the midline. Roentgen examination of the gastrointestinal tract revealed no significant findings. A diagnosis of pancreatic cyst was made.

At operation performed by one of us (J. R.) there was found a small cyst arising from the midportion of the body of the pancreas. The cyst was excised,

and the abdomen was closed. Grossly, the specimen consisted of a multiloculated cyst 5 cm. in diameter. The wall was thin, and the contents consisted of a pale green watery fluid. Microscopically, the cyst wall was composed of loose bands of fibrous connective tissue which was thrown into numerous papillary folds lined by cuboid epithelium. In places the epithelium was heaped up and formed several layers of cells (fig. 3).

Chemical analysis of the cystic fluid revealed the presence of amylase.

Retention cyst of the pancreas is usually small and of little clinical or pathologic significance. It is said to arise as a result of obstruction



Fig. 3.—Photomicrograph showing cystadenoma of the pancreas. The section shows a multiloculated cyst lined by cuboid epithelium with many papillary projections also lined by cuboid cells.

to the pancreatic duct caused by calculi, tumor or chronic pancreatitis. In the necropsy records of the hospital we were able to find 2 cases of retention cyst of the pancreas in which operation was not done.

CASE 14.—R. L., a 70 year old woman, was admitted to the hospital because of cardiac failure and general arteriosclerosis. She died shortly afterward, and at autopsy there was found in addition to cardiac hypertrophy a small cyst in the pancreas. The wall was thin and translucent, and the contents consisted of a cloudy pale yellow fluid.

Microscopically, the cyst wall was observed to be composed of loose fibrous tissue partly covered on its inner surface with flat epithelium (fig. 4).

CASE 15.—W. R., a 76 year old man, entered the hospital with the diagnosis of coronary thrombosis. He died several days later. At autopsy there were found in addition to coronary thrombosis and myofibrosis cordis multiple cysts of the pancreas. Microscopically the cyst walls were observed to be made up of a layer of fibrous connective tissue lined on one side by a single layer of low epithelium. The rest of the pancreas showed marked fibrosis.

The embryologic development of the pancreas and the morphologic relation of the pancreas to neighboring structures are of unquestioned significance in the production of certain forms of pancreatic cyst. From



Fig. 4.—Photomicrograph showing retention cyst of the pancreas. Much of the epithelium lining the cyst is denuded and thrown into the cavity of the cyst. The rest of the cyst wall consists of a thin layer of loose fibrous tissue.

the embryologic standpoint it is conceivable that remnants of duodenal tissue can become lodged within the pancreas. It is also possible for portions of these embryonic structures to migrate in the retroperitoneal tissues to invade the pancreas and act as nuclei of pancreatic tumors in postnatal life. Maldevelopment in the form of misplaced portions of Brunner's glands or irregularities in the normal differentiation of cells has not been seen. However, when such a condition does arise, obstruction of these glands may lead to cyst formation, in which acini or even an entire lobule may be dilated and contain a mass of cell detritus with

varying amounts of mucin. This hypothesis explains the similarity in cell structure of these cysts in the pancreas to Brunner's glands. More rarely there occur large cysts reaching several millimeters in diameter and producing nodules in the pancreas. The cysts are lined with low cuboid epithelium, and the lumens are largely free from stainable substances.

It seems reasonable in view of what has been said to assume that cysts of the pancreas may also arise from misplaced Brunner's glands in the pancreatic tissue. As an illustration of such a possibility we cite the following case:



Fig. 5.—Photomicrograph showing Brunner's gland cyst of the pancreas. The innermost lining of the cyst is thrown into numerous folds lined by columnar mucous secreting epithelium. Immediately under this are islands of Brunner's glands and a thin layer of loose connective tissue. Scattered islands of Brunner's glands also are found within the pancreas.

CASE 16.—D. F., a 42 year old man, died as a result of aortic stenosis and cardiac failure. A cyst of the pancreas was an incidental finding at necropsy. Grossly, the cyst was seen to be thin walled and located in the tail of the pancreas. On section clear serous fluid escaped. Microscopically, the cyst wall was observed to be made up of a delicate layer of connective tissue lined on the inside by a single layer of tall columnar epithelium. Immediately subjacent to the epithelial layer there were found at irregular intervals mucinous glands similar in appearance to Brunner's glands. Similar glandular structures were found also in the pancreas away from the cyst (fig. 5).

Cases reported in the literature and our own cases show that pancreatic cyst is usually a benign lesion. This, however, does not prove that the cyst may not be a precursor of carcinoma. The following case shows that carcinoma may develop secondary to cystic degeneration. It even seems possible that in some cases the rare primary adenocarcinoma of the pancreas develops on the basis of cystadenoma or pseudocyst of the pancreas. It is doubtful, however, whether this justifies calling cyst of the pancreas a precancerous lesion.

CASE 17.—S. S., a 69 year old woman, was admitted to the hospital because of itchiness of the skin, abdominal distress and loss of weight. She dated the

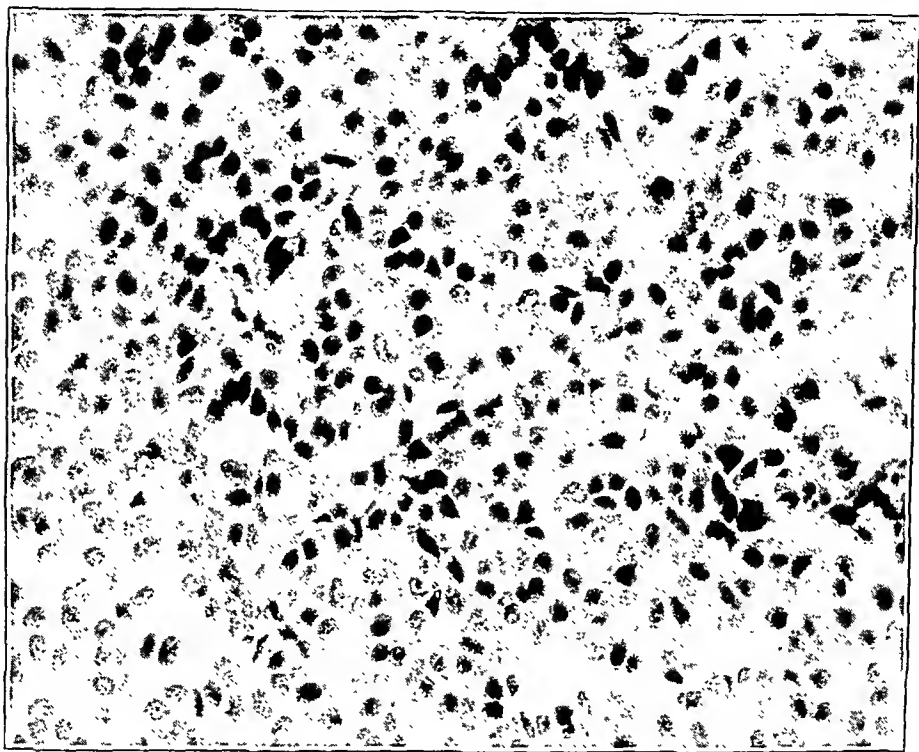


Fig. 6.—Photomicrograph showing pseudocyst of the pancreas with carcinomatous degeneration. Section shows sheets of tall cylindric cells occasionally grouped around a central lumen. There are few mitotic figures.

onset of her illness to six months previously, when she first complained of fulness in the epigastrium and nausea after eating. This lasted for a month, and the condition subsided. Two months later a heavy sensation in the epigastrium after eating again developed and was relieved by vomiting. Two months before admission the urine was turning dark in color; the stools were clay colored, and the patient became jaundiced. She was known to have diabetes for the last four years before admission, which was well controlled by diet. A lump had been felt in the epigastrium for the last two years; it had been gradually increasing in size in recent months.

On examination the patient was jaundiced and emaciated. The abdomen presented a tender freely movable mass just to the right of the epigastrium which extended as far as the umbilicus and posteriorly toward the spine. Roentgen examination revealed that there was a deviation of the pylorus and a marked increase in the duodenal sweep with a narrowing of the lumen of the duodenum. It was suggested that the duodenal sweep embraced a tumor in the head of the pancreas. There was some obstruction to the outflow of barium sulfate from the stomach. The blood sugar varied between 100 and 276 mg. per hundred cubic centimeters; the icteric index was 111. The clinical diagnosis was carcinoma of the head of the pancreas.

At operation performed by one of us (J. R.) a large retroperitoneal cystic mass about 20 cm. in diameter was found to be located in the region of the head of the pancreas. Numerous dilated veins coursed over the free surface of the tumor. The gallbladder was thick walled and distended with thick dark bile; it was free of calculi. The wall of the cyst was incised, and about 2,000 cc. of sanguineous fluid was aspirated. In the belief that this was a pseudocyst of the pancreas, the cyst wall was marsupialized after a small portion had been removed for pathologic examination.

Biopsy showed the cyst wall to consist of sheets and nests of tall cylindric epithelium which varied somewhat in shape, size and staining characteristics. The nuclei were spherical or ovoid and in places vesicular and hyperchromatic. There were relatively few mitotic figures. In places the cells were grouped around a central lumen, simulating glandular formation. The cytoplasm of the cells was abundant and granular. The stroma was scant and composed of hyalinizing connective tissue enclosing thin-walled engorged blood vessels and a small number of round cells (fig. 6).

#### COMMENT

The clinical picture presented by this group of cases of pancreatic cyst merits some detailed description, though in many respects the cysts followed the pattern previously described by many authors. The diagnosis of these tumors is beset at times with many difficulties. The early symptoms and signs are by themselves not distinctive and are similar to those associated with other intra-abdominal lesions. In certain cases the difficulties in arriving at a diagnosis may appear insurmountable. The laboratory tests, although of great value, are by no means infallible.

Table 2 summarizes the salient data of our cases. Analysis of the diagnostic facts relating to this disease shows that pain is the most important subjective symptom. It was present in all of the operative cases, and varied from a sensation of fulness to sharp abdominal cramps. The location of the pain varied. In 6 patients the pain was localized in the epigastrium; in 2, in the lower part of the abdomen; in 1, in the left upper quadrant of the abdomen, and in the remaining patients the pain was diffuse throughout the abdomen. In many instances the pain was associated with nausea and vomiting.

Loss of weight occurred in 6 of the patients operated on; constipation, in 5, and diarrhea, in 2. Jaundice occurred in 3 patients. Of



TABLE 2.—Summary of Salient Data of Seventeen Cases of Pancreatic Cyst

Case	Age and Sex of Patient	Duration of Symptoms	Symptoms	Jaundice	Constipation	Diarrhea	Loss of Weight	Nutrition	Location of Mass	Preoperative Diagnosis	Postoperative Diagnosis	Chemical Composition of Cystic Fluid
1	56 ♀	3 yr.	Cramps	No	No	No	Yes	Emaciated	Pelvis	Retropertitoneal tumor	Pseudocyst of pancreas	Mucus, diastase and trypsin
2	35 ♀	6 mo.	Pressure in epigastrium; vomiting	No	No	No	Yes	Good	Left hypogastrium	Omental or pancreatic cyst	Pseudocyst	Not determined
3	47 ♀	2 weeks	Abdominal pain; vomiting	No	No	No	Yes	Good	None	Pancreatic tumor	Pseudocyst	Trypsin and fat
4	21 ♀	6 mo.	Enlarging abdomen	No	Yes	No	No	Good	Left side of abdomen	Cyst of ovary	Pseudocyst	Amylase
5	23 ♀	5 days	Epigastric distress; vomiting	No	Yes	No	No	Good	Left upper quadrant of abdomen	Chronic appendicitis	Pseudocyst	Amylase
6	31 ♀	8 mo.	Pain in left upper quadrant of abdomen	No	No	Yes	No	Good	Right upper quadrant of abdomen	Cyst of pancreas	Pseudocyst	Amylase
7	41 ♀	6 mo.	Abdominal pain	No	No	No	No	Obese	None	Cyst of pancreas; retropertitoneal sarcoma	Pseudocyst	Amylase and trypsin
8	49 ♀	5 mo.	Pain in left upper quadrant of abdomen	No	Yes	No	Yes	Obese	Right upper quadrant of abdomen	Cyst of pancreas	Pseudocyst	Amylase and lipase
9	23 ♀	3 mo.	Fulness in epigastrium	No	Yes	No	No	Good	Pelvis	Acute pancreatitis	Pseudocyst	Amylase and blood
10	48 ♀	4 mo.	Acute abdominal pain; vomiting	Yes	No	No	No	Good	None	Acute cholecystitis	Pseudocyst	Amylase, lipase and bile
11	72 ♀	6 weeks	Abdominal pain	Yes	No	No	Yes	Good	Left upper quadrant of abdomen	Carcinoma of pancreas	Pseudocyst	Not determined
12	28 ♂	2 days	Pain in lower part of abdomen; blood in stools	No	No	No	No	Good	None	Peptic ulcer	Cystadenoma of pancreas; duodenal ulcer	Not determined
13	45 ♀	5 mo.	Epigastric distress	No	No	No	No	Good	Left upper quadrant of abdomen	Cyst of pancreas	Cystadenoma of pancreas	Amylase
14	70 ♀	.....	Asthma	No	No	No	No	.....	None	Arteriosclerosis	Retention cyst	Not determined
15	76 ♂	.....	Coronary thrombosis	No	No	No	No	.....	None	Coronary thrombosis	Retention cysts	Not determined
16	42 ♂	.....	Cardiac failure	No	No	No	No	Good	None	Cardiac failure	Inclusion cyst of pancreas	Not determined
17	69 ♀	6 mo.	Epigastric distress; nausea; mass	Yes	Yes	Yes	Yes	Emaciated	Right upper quadrant of abdomen	Carcinoma of head of pancreas	Cyst; carcinoma of pancreas	Blood; no ferments

121 cases reported by Körte, jaundice occurred in 9. Two of the patients with jaundice in our series had attacks of acute cholecystitis shortly before the discovery of the pancreatic cyst; the third patient with jaundice had a cyst of the head of the pancreas with carcinomatous degeneration.

Practically all the patients operated on presented past histories which may have had bearing on their illness. Thus they all experienced transient attacks of pain which varied in duration from two days to three years; the average duration of symptoms was about six months. Since trauma, cholecystitis and pancreatitis are frequently associated with formation of cyst of the pancreas, these must be considered in evaluating the symptoms of this disease. Two of the patients in this series had attacks of cholecystitis, and 1 had an attack of acute pancreatitis before the cyst developed in the pancreas. None of the patients, however, gave a history of trauma prior to the onset of illness. Three of the patients felt a gradually increasing swelling in the abdomen; in 1 instance the swelling was felt for two years, and at operation the lesion proved to be a pseudocyst with carcinomatous degeneration. In the group of cases in which operation was not done, the cysts were small and yielded no clinical evidence of their presence.

Physical examination revealed that 10 patients were well nourished, that 2 were obese and that 2 were emaciated. Only 3 patients appeared acutely ill on entering the hospital. Tenderness over the affected area was elicited in 5 patients.

Pseudocystic tumor usually presented itself as a large semifluctuant mass. In 4 cases it was located in the left upper quadrant of the abdomen; in 3, in the right upper quadrant of the abdomen; in 2, in the lower part of the abdomen, and in 1 case the mass occupied the entire left side of the abdomen. A mass was felt in 114 of the 121 cases which Körte reviewed from the literature. In 45 of the 47 cases reported by Judd, Mattson and Mahorner,<sup>8</sup> more than 95 per cent, the tumor was felt above the umbilicus. In 21 cases the tumor was to the left of the median line; in 11, approximately in the median line, and in 13, to the right of the median line. In 1 case the tumor was felt in the pelvis and was found enclosed in the mesentery of the sigmoid.

Cysts of the pancreas as a rule are relatively immobile. They are more apt to be freely movable when situated in the tail of the organ. Mobility of the cyst was noted in 6 cases of the present series; in 3 the cyst was described as ballotable, and in 3 others it was said to be moving freely with respiration.

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8. Judd, E. S.; Mattson, H., and Mahorner, H. R.: Pancreatic Cysts: Report of Forty-Seven Cases, *Arch. Surg.* 22:838 (May) 1931.

Roentgen examination is a major aid in the diagnosis of cyst of the pancreas. An enlarged duodenal curve is characteristic of enlargement in the region of the head of the pancreas. So too, displacement of the duodenum and the small intestine points toward the diagnosis of cyst of the pancreas. In 6 of the patients, roentgen examination revealed the presence of a mass in the region of the pancreas. When the head of the pancreas was the seat of the tumor, definite changes in the angle of the duodenum were observed.

The preoperative diagnosis was cyst of the pancreas in 4 cases, carcinoma of the pancreas in 2, retroperitoneal tumor in 1, omental or pancreatic cyst in 1, ovarian cyst or fibromyoma of the uterus in 1, peptic ulcer in 1, acute pancreatitis in 1, acute cholecystitis in 1, chronic appendicitis in 1 and retroperitoneal sarcoma or cyst of the pancreas in 1.

The pathologic picture presented at operation is characteristic. The large cyst arising from the region of the pancreas is so striking that one can scarcely fail to diagnose the condition at operation after having once viewed the lesion. The tumor usually presents itself as a smooth, relatively immobile, hemispheric and semifluctuant swelling, arising in the region of the pancreas. On aspiration, it yields a sanguineous fluid. One of the cysts in the series had globules of oil in addition to blood, and another showed the presence of bile. The size of the tumor in this series varied from 5 to 30 cm. in diameter. In 3 instances the tumor extended into the pelvis and contained several liters of fluid.

The existence of pancreatic secretions in the cyst has been frequently noted. On the other hand, numerous instances of true cysts are on record in which no ferments were found. To confirm or exclude the diagnosis of pancreatic cyst, the absence of ferments therefore appears to be of relatively little value. Chemical analysis of the aspirated fluid in our series revealed that 10 of the examined specimens showed the presence of trypsin, amylase or both. In 6 instances no chemical analysis was done, and in the case of pseudocyst with carcinomatous changes no enzymes could be found in the aspirated fluid. Some of the cysts also contained mucus, fat, bile and lipase.

The histologic descriptions in the literature are similar to those in our cases. It seems unnecessary to repeat the histologic picture in detail, but a few points might be reemphasized. In the cases of pseudocyst, the wall was made up almost entirely of dense layers of fibrous connective tissue lined on the inner surface with a single layer of cuboid epithelium. In many instances an epithelial covering was entirely absent. At no time was there found pancreatic tissue in the wall of the cyst, thus indicating that the origin of the cyst was probably extra-pancreatic (fig. 2).

Cystadenoma represents the true form of pancreatic tumor. This type of neoplasm is not common; it occurred in 2 cases of the present

series. The lesion was characterized by a rich papillary formation arising from the inner lining of the cyst. Each papilla was composed of a thin stalk of fibrous tissue lined by one or several layers of epithelial cells (fig. 3).

Retention cyst of the pancreas is in all probability a result of some form of obstruction to the pancreatic duct. In the cases cited the cyst wall was thin and lined by a single layer of cuboid or flat epithelium (fig. 4).

Inclusion cysts develop in the pancreas from cells which are not normally there but which were incorporated in the organ from some extraneous tissue by a faulty development in embryonal life. Slight flaws in the embryologic development, which are frequent, would be sufficient to explain the possibility of retention of Brunner's glands in the adult pancreas. This hypothesis also explains the similarity between the glands found in the pancreas to those of Brunner's glands. These glands are enclosed within the pancreas, and the formation of cysts may occur because the epithelium is found to be secreting. Their great rarity makes it improbable that every pancreas under certain circumstances harbors these glands. In the case reported here the cyst was lined by tall columnar epithelium similar in appearance to the cells lining Brunner's glands. In addition there were found in the pancreas mucinous glands of the Brunner type both in the immediate vicinity of the cyst and at some distance from it (fig. 5).

Pseudocyst of the pancreas with carcinomatous degeneration is of rare occurrence. Mahorner and Mattson<sup>9</sup> reported 4 cases of carcinomatous cyst among 88 patients with pancreatic cyst treated surgically at the Mayo Clinic. It occurred in 1 case in our series. The tumor is usually slow growing, and, as far as our knowledge goes, metastases have not been observed even when a large primary tumor was present for a long time. The tumor reported was apparently present for two years before the patient sought medical advice. Microscopic examination of the cyst showed it to be a relatively slow growing neoplasm (fig. 6).

Choice of operation depends on the size, the variety, the situation and the condition of the cyst. The ideal treatment is complete removal, if possible. Small cysts, especially when in the tail of the pancreas, should be excised. In cases in which the cyst is large and adherent, marsupialization of the tumor is the method of choice.

Little need be said of the prognosis in cases of pancreatic cyst. Benign cystic growths can be removed with only a slight mortality rate, whereas malignant tumors in the pancreas, like those in other locations, permit only a poor prognosis.

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9. Mahorner, H. R., and Mattson, H.: Etiology and Pathology of Cysts of Pancreas, *Arch. Surg.* **22**:1018 (June) 1931.

## SUMMARY

Seventeen cases of primary cyst of the pancreas are reviewed. In 11 of these the lesion was pseudocyst; in 2, cystadenoma; in 2, retention cyst; in 1, inclusion cyst, and in 1, pseudocyst with carcinomatous degeneration.

The diagnosis of pancreatic cysts is difficult at times, but, given a large cystic mass extrinsic to the gastrointestinal tract, the possibility of cyst should be borne in mind. Roentgen examination is of considerable help in making a diagnosis.

The presence or absence of pancreatic enzymes in the cyst fluid is not pathognomonic of the disease.

From the embryologic point of view it is conceivable that certain pancreatic cysts may arise from misplaced remnants of Brunner's glands. Such a tumor is described in 1 of the cases presented.

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# POSTOPERATIVE CHYLOTHORAX

## SUDDEN DEATH FOLLOWING THE INFUSION OF ASPIRATED CHYLE

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AND

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Within the year an excellent article on traumatic chylothorax appeared in this journal.<sup>1</sup> A cure was effected by the intravenous administration of the aspirated chyle. In contradistinction the present paper reports a case of postoperative chylothorax in which sudden death followed such intravenous administration of chyle. Our article further stresses: (1) the rarity of such a lesion; (2) the dangers of inadvertent section of the duct during sympathectomy operations for hypertension; (3) the precautions to be taken following such a mishap, and (4) the possible cause of such sudden death.

### LITERATURE

This is the first case to be reported of inadvertent sectioning of the thoracic duct during the course of a sympathectomy operation. It is the second case to be reported of such sectioning during the course of any operation. Indeed, chylothorax from any trauma is a rare condition. Shackelford and Fisher<sup>2</sup> collected 43 authentic cases. Nowak and Barton,<sup>3</sup> Smith and Woliver,<sup>1</sup> Dorsey and Morris<sup>4</sup> and Little, Harrison and Blalock<sup>5</sup> each added another case. In the majority of cases the condition was caused by injuries within the lower part of the thoracic cage. The mortality rate averaged 50 per cent in the total series.

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From Hartford Hospital.

1. Smith, D. D., and Woliver, E.: Traumatic Chylothorax, *Arch. Surg.* **43**: 627-632 (Oct.) 1941.

2. Shackelford, R. T., and Fisher, A. M.: Traumatic Chylothorax, *South. M. J.* **31**:766-775 (July) 1938.

3. Nowak, S. J. G., and Barton, P. N.: Chylothorax, *J. Thoracic Surg.* **10**: 628-634 (Aug.) 1941.

4. Dorsey, J. F., and Morris, C. G.: Traumatic Rupture of the Thoracic Duct with Chylothorax, *J. A. M. A.* **119**:337-338 (May 23) 1942.

5. Little, J. M.; Harrison, C., and Blalock, A.: Chylothorax and Chyloperitoneum, *Surgery* **11**:392-401 (March) 1942.

There have been only 5 cases<sup>6</sup> in which treatment consisted of intravenous injection of the aspirated chyle. Two patients died; 2 recovered, and 1 remained in status quo. In 1908 Oeken<sup>6a</sup> first reported the use of this method with a fatal result. In 1937 Bauersfeld<sup>6b</sup> first cured 1 patient by the direct transfer of intrathoracic chyle into the basilic vein. In this journal in October 1941, Smith and Woliver<sup>1</sup> recorded another case in which treatment by four indirect transfusions of chyle of approximately 750 to 1,000 cc. each was successfully carried out. The chyle was collected in citrate, cultured for sterility and refrigerated for twenty-four hours or longer. Since then Dorsey and Morris<sup>4</sup> have reported a case in which the patient died despite the infusion of chyle. Little, Harrison and Blalock<sup>6</sup> recently published a comprehensive report of a case in which combined chylothorax and chyloperitoneum developed in a 17 year old girl, probably secondary to traumatic thrombophlebitis of the left internal jugular vein. At the time of the report (March 1942) the phenomenal total of approximately 540 liters of chyle had been removed over a period of eighteen months by peritoneal and left pleural taps. This constituted an average of 1,000 cc. a day. Approximately 22,500 cc. of this chyle was reinfused over the first six month period. None was reinfused over the ensuing twelve month period. The authors noted no improvement following the chylous transfusions. At the time of writing the patient was still alive.

#### SIGNS AND SYMPTOMS

In all cases of chylothorax, whether traumatic, operative or spontaneous, there are: (1) a history of delayed onset, generally from the seventh to the tenth day following the known severance; (2) a rather sudden onset of dyspnea; (3) continuing respiratory embarrassment with mild shock; (4) massive intrathoracic chyle (as much as 3,500 cc.), generally on the right side; (5) the necessity for frequent thoracenteses (as often as twice daily); (6) spontaneous healing and sealing of the severed duct in from seven to twenty-one days, provided the patient survives (Little's case<sup>6</sup> is in contradistinction to this); (7) emaciation from the lowering of serum protein and to a lesser extent of the serum lipoids; (8) a 50 per cent mortality rate from inanition rather than respiratory embarrassment.

#### FUNCTION

The thoracic duct starts just anterior to the second lumbar vertebra and passes through the aortic hiatus of the diaphragm just anterior and

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6. (a) Oeken: Ein Fall von Zerreissung des Ductus thoracicus infolge Brustquetschung, München. med. Wchnschr. 55:1182-1183, 1908. (b) Bauersfeld, E. H.: Traumatic Chylothorax from Ruptured Thoracic Duct Treated by Intravenous Injection of Aspirated Chyle, J. A. M. A. 109:16-18 (July 3) 1937. (c) Shackelford and Fisher.<sup>2</sup> (d) Dorsey and Morris.<sup>4</sup> (e) Little, Harrison and Blalock.<sup>6</sup>

to the right of the aorta. In ascending the thorax it slowly shifts to the left, ultimately joining the left subclavian vein. This course shows some variation in 27 per cent of the cases.<sup>7</sup> Sixty per cent of the digested fat passes through this duct with as much as 130 to 195 cc. of chyle entering the veins of the neck each hour. The protein content ranges from 1 to 6 Gm. per hundred cubic centimeters. The fat content varies from 0.4 to 2.8 cc. per hundred cubic centimeters. The chyle is alkaline in reaction and contains a high percentage of lymphocytes. In cases of chylothorax there is a consequent decrease of lymphocytes in the circulating blood. On settling the chyle has three layers: a cream layer on top, a milk layer in between and a cellular sediment layer on the bottom. In most of the cases it has been reported as sterile.

The treatment of chylothorax is aimed at satisfying two chief requirements: (1) the prevention of respiratory embarrassment and (2) the maintenance of nutrition. Only enough chyle has been removed to permit adequate respiratory function. Further removal apparently stimulates further leakage. Refeeding of the aspirated chyle by mouth has not been of benefit. In recent years the chyle has been replaced, first by direct<sup>8</sup> and then by indirect infusions.<sup>9</sup> In the case of Smith and Woliver the aspirated citrated chyle was allowed to stand from one to four days before use. No harmful reactions were noted. Nowak,<sup>10</sup> in Boston, has used this same method in experimental work on dogs and has advised the use of such a method in clinical practice. The intravenous administration of heterogenous fats emulsified by the Yamakawa method has been used in pediatric practice by Holt and associates<sup>11</sup> without reactions. Gildea<sup>12</sup> has had 1 severe reaction but no fatality (with its use in the treatment of psychiatric patients).

There is general agreement that no attempt should be made to reoperate in an effort to repair the duct. Exposure is most difficult.

#### REPORT OF CASE

A. T. P., a 39 year old small, almost emaciated, woman, was admitted to Hartford Hospital on Aug. 28, 1941, because of precordial pain, nervousness, weakness and underweight. She weighed only 89 pounds (40.4 Kg.) and on examination was found to have grade 2 essential hypertension with a blood pressure of 210 systolic and 140 diastolic. Nonprotein nitrogen, basal metabolic rate, intra-

7. Davis, H. K.: A Statistical Study of the Thoracic Duct in Man, *Am. J. Anat.* **17**:211-244, 1914.

8. Little, Harrison and Blalock.<sup>5</sup> Bauersfeld.<sup>6b</sup>

9. Smith and Woliver.<sup>1</sup> Bauersfeld.<sup>6b</sup>

10. Nowak, S. J. G.: Personal communication to the authors.

11. Holt, L. E., Jr.; Tidwell, H. C., and Scott, T. F. McN.: The Intravenous Administration of Fat, *J. Pediat.* **6**:151-160 (Feb.) 1935.

12. Gildea, E. F.: Personal communication to the authors.



venous pyelogram, cardiac outline, chest plate, gastric analysis, blood, urine and stool analyses were all normal. She exhibited signs of grade 2 hypertensive retinopathy (Wagener and Keith classification) and showed an excellent fall in blood pressure (to 120 systolic and 90 diastolic) following the various sedative tests. She was deemed a good candidate for transdiaphragmatic sympathectomy to be done in two stages according to the method of Smithwick.<sup>13</sup>

On October 20 sympathectomy was done on the right side. After the twelfth rib was removed and the diaphragm was split, the right splanchnic nerves as well as the chain were visualized and resected from approximately the tenth dorsal down to and including the second lumbar sympathetic ganglion.



Fig. 1.—Roentgenogram showing the location of clips on cut ends of the thoracic duct.

At operation the extraordinary emaciation of this patient was noted. The entire posterior and lateral surfaces of the aorta and the anterior surface of the vertebral bodies could be easily visualized. In an effort to remove the aortic and lesser branches of the splanchnic nerve the thoracic duct at the level of the first lumbar vertebra was exposed and inadvertently torn. The duct was promptly recognized as such. No attempt was made to suture it, but it was doubly clipped with two silver clips placed tightly on both the distal and the proximal end (fig. 1). A small portion was examined microscopically; this proved it to be a tube lined with epithelial cells.

13. Smithwick, R. A.: A Technique for Splanchnic Resection for Hypertension, *Surgery* 7:1-8 (Jan.) 1940.

The operation was concluded without complications. The early convalescence was uneventful with a blood pressure of 140 systolic and 90 diastolic. But at the end of one week the patient looked worse, and some respiratory embarrassment had developed. A chest film revealed a small amount of fluid at the base of the right lung. On the fourteenth postoperative day the patient experienced a sudden onset of severe dyspnea and cyanosis and exhibited flatness over the entire right side of the chest, with complete opacity to roentgen rays (fig. 2); 2,150 cc. of cream-colored pinkish fluid was removed by thoracentesis. It coagulated on standing. A direct smear showed many white blood cells with 80 per cent lymphocytes as well as fat globules by sudan III stain. No bacteria were seen on smear or



Fig. 2.—Roentgenogram of the thorax taken on the fourteenth postoperative day, showing complete obliteration of the right lung filled by chyle.

culture. A repeat thoracentesis on the sixteenth postoperative day yielded 1,500 cc. of chyle. The patient's general condition was bad; she was considerably weakened. The serum protein had dropped to 5 Gm. per hundred cubic centimeters and the white blood cell count to 3,500 with a decrease chiefly of lymphocytes. On the seventeenth postoperative day 1,500 cc. of additional chyle was aspirated. The patient became weaker, and the serum protein fell alarmingly to 3.8 Gm. per hundred cubic centimeters with a blood calcium content of 7.9 mg. per hundred cubic centimeters. Transfusions of blood and plasma on the sixteenth and seventeenth days caused general improvement and a rise in the serum protein content to 4.3 Gm. per hundred cubic centimeters.

In line with the work of Bauersfeld<sup>6b</sup> and Smith and Woliver<sup>1</sup> as well as the verbal advice of Nowak<sup>10</sup> it was decided to replace the aspirated chyle by a delayed citrated infusion. Eight hundred and fifty cubic centimeters of chyle was aspirated aseptically by the closed method in a citrated blood transfusion outfit. It was placed in a refrigerator, and a sample was taken for culture which proved sterile after twenty-four hours. The chyle was then given fractionally by the gravity method. Ten cubic centimeters was first given slowly in solution of sodium chloride without reaction; following this administration of the main amount was started slowly at the rate of approximately 200 cc. per hour. After 75 cc. had run in, a chill developed. The infusion was immediately stopped, but the chill grew worse and was accompanied by true asthmatic breathing, generalized shock and a sense of impending death. The patient was placed in extreme shock position; her legs were elevated and bandaged with elastica bandages. Epinephrine was given intravenously. She experienced temporary relief, especially from the asthmatic breathing and the cyanosis. In a few minutes, however, the asthma returned. She again became cyanotic and gasping and died, notwithstanding the administration of more epinephrine. Permission for autopsy was refused.

#### COMMENT

This presentation of a tragic series of mishaps culminating in death is presented because of the following unusual features:

1. For the first time in our experience, as well as in the voluminous sympathetic literature, the thoracic duct was exposed and inadvertently torn while sympathectomy was being done for hypertension. The patient's extreme emaciation made her vulnerable.

2. Delayed chylothorax occurred even though the thoracic duct had been doubly closed with four silver clips, two on either end (fig. 1). In all probability the pressure of chyle within this duct is far greater than one would expect from the experimental work of Mouchet<sup>14</sup> and Blalock, Cunningham and Robinson.<sup>15</sup> Consequently either from erosion or from simple pressure the proximal end reopened at approximately seven to ten days.

3. Extreme caution and care must be exercised if intravenous administration of chyle is to be used. This patient died promptly from what appeared to be anaphylactic shock. She exhibited asthma, dyspnea, cyanosis, chills and shock momentarily improved by epinephrine and occurring within minutes of the start of infusion. Without autopsy it is impossible to differentiate conclusively between anaphylaxis, fat embolism and a foreign protein reaction. The clinical picture is most suggestive of the first. In 1 previous fatal case the patient also died suddenly after

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14. Mouchet, A.: Le chylothorax traumatique, *J. de chir.* **42**:386-399 (Sept.) 1933.

15. Blalock, A.; Cunningham, R. S., and Robinson, C. S.: *Experimental Production of Chylothorax by Occlusion of Superior Vena Cava*, *Ann. Surg.* **104**:359-364 (Sept.) 1936.

the infusion of autogenous chyle <sup>6a</sup> and at autopsy showed diffuse hemorrhagic exudate over the viscera and asphyxia, suggesting anaphylaxis. The other more recently reported death <sup>4</sup> was apparently due to inanition. Of the 6 cases in the literature in which this therapy was administered, death occurred in 3.

Necessary precautions in the future will consist of: (1) a careful test for sensitivity followed by a slow administration of 5 to 10 cc. intravenously and a delay of thirty minutes before starting the infusion proper; (2) microscopic measurements of the size of the fat globules with rejection of specimens containing globules of a diameter over 3 microns; <sup>11</sup> (3) twenty-four hour culture of the chyle (Little and associates <sup>5</sup> recommended direct infusion using a closed system with a three way stopcock); (4) in cases in which the chyle fails to meet the aforementioned standards, the intravenous use of plasma and of emulsified fats <sup>11</sup> with daily aspiration of the chyle; (5) in cases in which chylothorax persists after one week of this regimen, phrenicectomy as reported by Nowak and Barton; <sup>3</sup> (6) intravenous infusion of fat and protein to be done at an early date to prevent rapidly progressive emaciation.

#### SUMMARY

A review is made of the literature on chylothorax.

A report is presented of a case of chylothorax following sympathectomy for hypertension. Sudden death followed the intravenous administration of autogenous chyle in this case.

Precautions against the future occurrence of death are listed and methods of therapy are suggested.

179 Allyn Street.

# SODIUM SALTS OF THE SULFONAMIDE COMPOUNDS

A STUDY WITH SPECIAL REFERENCE TO THEIR LOCAL  
USE IN WOUNDS

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At present sulfanilamide is the accepted sulfonamide compound for local use in war wounds, compound fractures and the peritoneum.<sup>1</sup> Experiments in vitro, however, have clearly shown that sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) are more potent antibacterial agents than sulfanilamide and are also far more resistant to drug inhibitors, such as paraaminobenzoic acid.<sup>2</sup> Actually, against *Escherichia coli* (frequently a participant in peritonitis following intra-abdominal wounds) 1 mg. of sulfathiazole or sulfadiazine can accomplish as much as 430 mg. of sulfanilamide. To obtain bacteriostasis, furthermore, in the presence of 1 mg. per hundred cubic centimeters of paraaminobenzoic acid (or similar inhibitor of drug action) 15 mg. per hundred cubic centimeters of sulfadiazine or sulfathiazole is required, whereas 6,280 mg. per hundred cubic centimeters of sulfanilamide is necessary! Clinical experience has also demonstrated the superiority of these newer drugs over sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine).<sup>3</sup> Nevertheless, these drugs have not supplanted sulfanilamide in local therapy. Why?

It has been assumed that the relatively high water solubility of sulfanilamide facilitates its ready penetration and spread throughout

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The drugs used in this study were provided by the Lederle Laboratories, Inc.

From the Department of Bacteriology, Columbia University College of Physicians and Surgeons.

1. Cloward, R. B.: War Injuries to the Head, *J. A. M. A.* **118**:267 (Jan. 24) 1942. Veal, J. R., and Klepser, R. G.: Local Use of Sulfanilamide Therapy in Surgical Infections, *Surgery* **10**:947 (Dec.) 1941.

2. Rose, H. M., and Fox, C. L., Jr.: A Quantitative Analysis of Sulfonamide Bacteriostasis, *Science* **95**:412 (April 17) 1942.

3. Long, P. H.: Sulfadiazine: 2-Sulfanilamidopyrimidine Analogue of Sulfanilamide, *J. A. M. A.* **116**:2399 (May) 1941. Trevett, G. I.; Nelson, R. A., and Long, P. H.: Studies on Sulfadiazine: II. Clinical Use of Sulfadiazine in the Therapy of Bacterial Infections, Other Than Pneumonia, *Bull. Johns Hopkins Hosp.* **69**:303 (Oct.) 1941.

the local area resulting in its rapid absorption into the circulation. Bick, however, reported that sulfanilamide itself when placed in wounds is not completely dissolved and absorbed and may act somewhat as a foreign body in delaying healing.<sup>4</sup> The poor water solubility, on the other hand, of sulfadiazine and sulfathiazole has made them appear unsuited for this purpose. Many observers have in fact reported on the poor absorption of these drugs following implantation in the rectus muscle<sup>5</sup> and in wounds.<sup>6</sup> Subsequently, Taylor<sup>7</sup> reported that three days after implantation of sulfathiazole and sulfadiazine "actual abscesses were formed about crystals which still persisted in the tissues." It seemed important, therefore, to study the properties of the soluble sodium salts of sulfathiazole and sulfadiazine to assess their suitability for local use in wounds and in the peritoneum to obtain the benefits of these superior, more effective antibacterial agents. It will be shown by actual experimentation that these salts are suitable for local use in wounds.

It seemed likely that this study might suggest also a means of preventing a not uncommon complication of chemotherapy, viz., renal precipitation of the free and acetylated drugs. This disadvantage has been associated with the relatively poor water solubility of sulfapyridine, sulfathiazole and sulfadiazine and has to some extent limited the systemic use of these potent chemotherapeutic agents. In view of the fact that when ionized (as are the sodium salts) their solubility is greatly increased, investigation of the physiologic possibility of inducing urinary excretion of these drugs in the form of their soluble salts might yield a method of preventing precipitation of these drugs in the kidney.<sup>8</sup>

#### COMPARATIVE ALKALINITY OF SOLUTIONS OF THE SODIUM SALTS OF THE SULFONAMIDE COMPOUNDS

Because of the not infrequent earlier experience that the extremely alkaline sodium sulfapyridine when allowed to leak under the skin during intravenous injection produced necrosis of the tissues followed

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4. Bick, E. M.: Topical Use of Sulfonamide Derivatives, *J. A. M. A.* **118**:511 (Feb. 14) 1942.

5. Long, P. H.: Clinical Use of Sulfonamide Compounds in Prophylaxis and Treatment of Infections, *Northwest Med.* **40**:311 (Sept.) 1941.

6. Hawking, F., and Piercy, J. E.: Blood Concentrations Following Local Applications of Sulfonamide Compounds to Wounds, *Brit. M. J.* **1**:511, 1941.

7. Taylor, F. W.: Misuse of Sulfonamide Compounds, *J. A. M. A.* **118**:955 (March 21) 1942.

8. Jensen, O., and Fox, C. L., Jr.: Factors Controlling Absorption and Renal Excretion of Sulfadiazine, to be published.

by sloughing, it has been supposed that sodium sulfathiazole (the sodium salt of 2-[paraaminobenzenesulfonamido]-pyridine) and sodium sulfadiazine (the sodium salt of 2-[paraaminobenzenesulfonamido]-pyrimidine) would do the same. Actually this is not the case. There are also numerous references in the literature to the high alkalinity of these sodium salts. For example, 10 per cent solution of sodium sulfathiazole has been assigned " $p_H$  10 to 11" and compared to 10 per cent solution of sodium hydroxide.<sup>9</sup> Because of "hydrogen ion concentration of approximately 10 to 11" these drugs have also been described as "irritating to an already sick peritoneum."<sup>10</sup> My measurements give much lower values. The  $p_H$ , for example, of 1 per cent solution of sodium sulfadiazine (twenty-fifth molar) is 8.66, and an equimolar solution of sodium bicarbonate has a  $p_H$  of 8.7 (table 1 and chart 1).

TABLE 1.—*Comparative Alkalinity of Solutions of the Sodium Salts of Sulfonamide Compounds*

Concentration of Solution	$p_H$ of Aqueous Solutions of the Sodium Salt of			
	Sulfapyridine	Sulfathiazole	Sulfadiazine	Carbonic Acid *
5.0 per cent.....	10.6	9.8	9.4	
2.5 per cent.....	10.3	9.6	9.3	
1.0 per cent.....	10.1	9.4	8.7	8.7
0.5 per cent.....	10.0	9.1	8.4	8.7
0.2 per cent (200 mg. per 100 cc.)	9.8	9.0	7.9	
100 mg. per 100 cc.....	9.7	8.7	7.6	
50 mg. per 100 cc.....	9.4	8.4	7.5	
10 mg. per 100 cc.....	8.4	8.0	7.3	

\* The solution of a sodium salt of carbonic acid used was an equimolar solution of sodium bicarbonate exposed to air.

Furthermore, solutions of the sodium salts of these drugs, like bicarbonate, are buffered by tissue fluids to the  $p_H$  of the blood. Thus, sodium sulfathiazole added to normal human plasma in a concentration of 100 mg. per hundred cubic centimeters raised the  $p_H$  of normal human plasma 0.1  $p_H$  unit. This same concentration of sodium sulfadiazine did not change the  $p_H$  of the plasma enough to register any increase with the sensitive glass electrode. Similar results were obtained with whole blood. In table 1 and chart 1 are comparisons of the alkalinity of

9. Fletcher, R.: The Caustic Action of Sodium Sulfathiazole, *J. A. M. A.* **117**: 1204 (Oct. 4) 1941; Application of Sulfonamide Compounds to the Nose, *ibid.* **118**: 998 (March 21) 1942. Reichert, F. L., in discussion on papers of Muller and Thompson and Jackson and Collier, *J. A. M. A.* **118**:200 (Jan. 17) 1942.

10. Province, W. D.: Sulfonamide Compounds—Their Uses and Principles of Therapy, *J. Indiana M. A.* **34**:659 (Dec.) 1941.

various solutions of the sodium salts of these drugs and of sodium bicarbonate. The results show that increasing the concentration of the drug from 1 to 5 per cent raises the  $p_H$  but slightly. Concentrations above 5 per cent are hypertonic and will be rapidly diluted by an influx of the tissue fluids.

In clinical practice at the Babies Hospital, New York, Dr. Gilbert M. Jorgenson demonstrated<sup>11</sup> that a 5 per cent aqueous solution of sodium sulfadiazine may be given subcutaneously (0.1 Gm. per kilogram of body weight) without clinical evidence of local tissue damage. More than forty hypodermoclyses were given; they were administered in the same subcutaneous area twice daily for more than one week. No local reaction was observed.

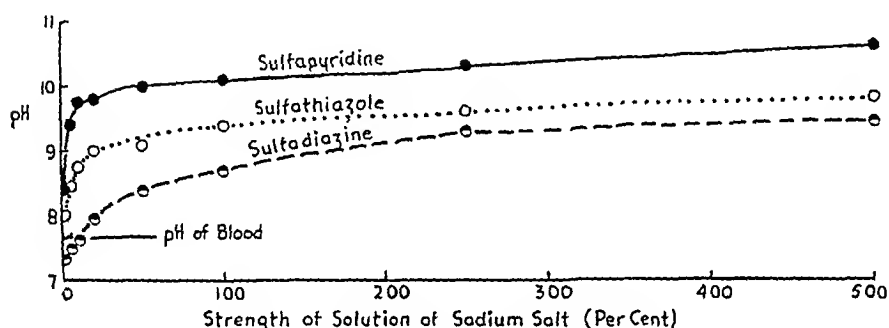


Chart 1.—The  $p_H$  of various strength solutions of the sodium salts of three derivatives of sulfanilamide.

#### DISSOCIATION OF THE SULFONAMIDE COMPOUNDS AND THE EFFECT OF THEIR IONIZATION ON THEIR SOLUBILITY

To obtain more complete comparative data, the dissociation constants of these drugs were measured. The  $p_K$  values obtained—that is the  $p_H$ <sup>12</sup> of an equimolar mixture of the drug (weak acid) and its soluble sodium salt—are given in table 2. Such data facilitate comparison of the relative acidity of these drugs and of other acids, e. g. carbonic and boric acids; these data are included in table 2 for comparison. The alkalinity of their sodium salts may likewise be gaged. Thus the most acidic drug, sulfadiazine, will have the least alkaline sodium salt. From these constants, furthermore, it is possible to estimate the relative amounts of each drug that exists in the ionized state at the  $p_H$  of biologic fluids (7.5). It is noteworthy (as shown in table 2) that in the body sulfa-

11. Jorgenson, G. M.: To be published.

12. All  $p_H$  measurements were made with the Beckmann glass electrode and vacuum tube potentiometer.



thiazole and sulfadiazine are almost completely ionized, whereas sulfanilamide is but slightly ionized. (The relation of this fact to the bacteriostatic potency of these drugs and to the effective blood level has been pointed out elsewhere.<sup>13</sup>)

In view of the relative acidity of sulfadiazine it seemed likely that its low water solubility might be increased in a physiologic buffer, in

TABLE 2.—*Comparative Acidity of Sulfonamide Compounds and Degrees of Ionization at the Hydrogen Ion Concentration of Biologic Fluids \**

Drug (Acid)	Acidity ( $pK$ )	Status at $pH$ 7.5	
		Ratio	Percentage Ionized in Form of Salt
Sulfanilamide.....	10.55	$\frac{1}{1,120}$	0.1
Boric acid.....	9.2	.....	...
Sulfapyridine.....	8.5	$\frac{1}{10}$	9.1
Sulfathiazole.....	6.8	$\frac{5}{1}$	83.4
Carbonic acid.....	6.55	.....	...
Sulfadiazine.....	6.4	$\frac{13}{1}$	92.9

\* Taken as  $pH$  7.5.

TABLE 3.—*Influence of Ionization on the Solubility of Sulfonamide Compounds*

Drug	Solubility in Water at 37 C., Mg. per 100 Cc.	Solubility in Fifteenth Molar Phosphate Buffer at 37 C., Mg. per 100 Cc.	Final $pH$ Attained	No. of Times Increase in Solubility in Phosphate Buffer
Sulfanilamide.....	1,400.0	1,720	7.30	1.2
Sulfaguanidine (sulfanilylguanidine)	190.0	235	7.42	1.2
Sulfapyridine.....	49.5	75	7.38	1.5
Sulfathiazole.....	94.0	248	7.36	2.6
Sulfadiazine.....	12.3	167	7.40	13.6

which it would exist in large proportions (table 2) as the extremely soluble ionized sodium salt. In these experiments a fifteenth molar phosphate buffer raised the solubility of sulfadiazine fourteenfold, as shown in table 3. Feinstone and associates<sup>14</sup> first reported on the

13. Fox, C. L., Jr., and Rose, H. M.: Ionization of Sulfonamides, *Proc. Soc. Exper. Biol. & Med.* **50**:142 (May) 1942.

14. Feinstone, W. H.; Williams, R. D.; Wolff, R. T.; Huntington, E., and Crossley, M. L.: Toxicity, Absorption and Chemotherapeutic Activity of 2-Sulfanilamidopyrimidine (Sulfadiazine), *Bull. Johns Hopkins Hosp.* **47**:427 (Dec.) 1940.

increased solubility of these drugs in biologic fluids. They furthermore determined

. . . that urea and sodium chloride are not responsible for the greatly increased solubility . . . Whether the apparent increase in solubility represents true solution or colloidal dispersion, especially in the blood, is not known, although it is believed that the latter possibility is rather remote.

In another study<sup>15</sup> the influence of dextrose and specific gravity was observed in an effort to explain this phenomenon. It is now apparent that these factors are insignificant and that the increased solubility in biologic fluids as in phosphate buffer must be largely, if not entirely, attributed to the formation of ionized soluble salts of these drug acids. In urine some solubility results from formation of soluble glucuronates.<sup>16</sup> These may arise secondarily from oxidation of the drugs in the body;<sup>17</sup> the hydroxyl derivatives then formed are subsequently conjugated with glucuronic acid. The significance of these data in relation to the absorption, the distribution and the excretion of this drug is at present under study.<sup>8</sup>

The important suggestion from these facts, however, is that since sulfadiazine and sulfathiazole occur in the body largely in the ionized form and since their sodium salts are only moderately alkaline, resembling sodium bicarbonate, the local use of these soluble salts seems to be worthy of trial.

#### EXPERIMENTS IN VIVO WITH SODIUM SALTS IN WOUNDS

Preliminary tests were carried out in mice and in dogs to determine whether the sodium salts are irritating to tissues and to ascertain the speed and the degree of their absorption into the general circulation.

White mice (weight, 20 Gm.) were anesthetized with ether; a 2 cm. incision was made into the muscles of the back, and 20, 40 or 50 mg. of the powdered sodium salts of sulfapyridine, sulfathiazole or sulfadiazine was placed in the pocket, which was then closed with black silk. The powder rapidly formed a uniform soft wet paste with the tissue fluid, some of the powder apparently dissolving quickly. There was no evidence of caking in the wound, and the time of healing was practically the same as in control mice. This is in marked contrast to similar

15. Curtis, A. C., and Sobin, S. S.: The Solubility of Acetyl-Sulfapyridine and Acetyl Sulfathiazole in the Urine, *Ann. Int. Med.* **15**:884 (Nov.) 1941.

16. Scudi, J. V.; Ratish, H. D., and Bullowa, J. G. M.: Increased Glucuronate Excretion Following Administration of Sulfapyridine, *Science* **89**:516 (June 2) 1939. Thorpe, W. V., and Williams, R. T.: Isolation of Acetylsulphathiazole from Human and Rabbit Urines Following Administration of M. & B. 760, *Nature*, London **146**:686 (Nov. 23) 1940.

17. Fox, C. L., Jr.: The Significance of the Oxidation of Sulfanilamide During Therapy, *Am. J. M. Sc.* **199**:487 (April) 1940.

experiments in which the acid forms of the drugs were used. The wounds in the mice that received sodium sulfapyridine showed a little more serous exudate than the controls; there was, however, no gross evidence of inflammatory reaction or necrosis. Microscopic sections taken eighteen hours after implantation showed disappearance of the drug with no chemical necrosis. A moderate degree of edema was present both in the control mice that received no drug and in the treated animals. The polymorphonuclear infiltration was but slightly less in the sections of the control mice. It should be noted that in these experiments the amounts of drug used represented doses of 70 to 150 Gm. in man.

These results were encouraging; but for comparison with Long's experiments<sup>5</sup> showing the poor absorption of sulfonamide acids, 0.24 Gm. of sodium sulfadiazine per kilogram of body weight<sup>18</sup> was placed

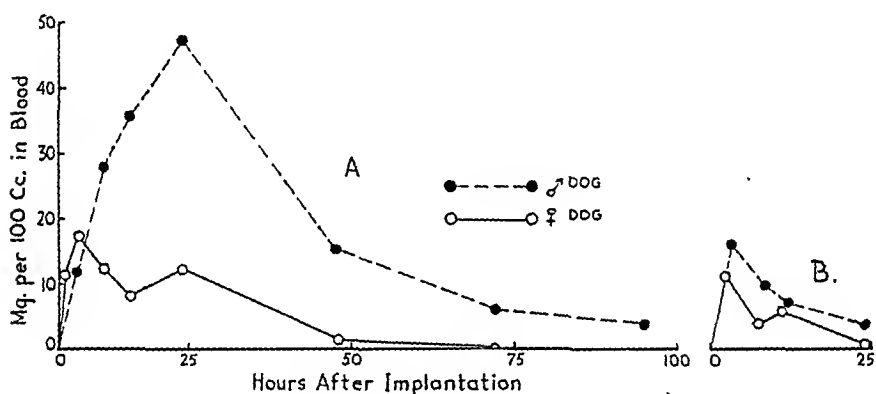


Chart 2.—*A*, the duration of absorption of sodium sulfadiazine powder (0.25 Gm. per kilogram of body weight) implanted in the rectus muscle. *B*, the duration of absorption of sodium sulfadiazine powder (0.1 Gm. per kilogram of body weight) placed in the peritoneal cavity.

into the rectus muscle and sheath of 2 dogs (3 and 5 Gm. respectively, equivalent to 17 Gm. in a man weighing 70 Kg.). The powder when placed into the wound formed a soft paste with the tissue fluids. It was necessary on account of the large volume of powder to compress it into the wound. This produced a localized swelling which existed beneath the skin for several days but which subsided, and the incision healed cleanly. There was no erythema or oozing from the wound to

18. The relatively low chronic toxicity of this drug is exemplified by observations that repeated intraperitoneal injection of 0.3 Gm. per kilogram of body weight in rats proved harmless (Lehr, D., and Antopol, W.: Toxicity of Sulfadiazine and Acetylsulfadiazine in Albino Rats with Special Reference to Renal Lesions and Their Significance, *Urol. & Cutan. Rev.* 45:545 [Sept.] 1941).

indicate irritation of the tissues or caustic action by the drug.<sup>19</sup> The concentration of sulfadiazine in the blood and the urine<sup>20</sup> was measured at intervals to ascertain the rates of absorption and excretion. The results as shown in chart 2 *A* indicate that absorption was rapid, resulting in good blood levels within two hours. Although the level declined after thirty hours, levels of several milligrams per hundred cubic centimeters persisted for fifty to a hundred hours. The high blood level in the male dog appears to be peculiar to this animal since subsequent oral administration of sulfadiazine in this dosage (0.25 Gm. per kilogram of body weight) to these same dogs resulted in blood levels around 38 mg. per hundred cubic centimeters in the thin long-boned male dog and around 13 mg. per hundred cubic centimeters in the fat short-boned female dog.<sup>5</sup>

Laparotomy was done on both dogs one week later, and 0.1 Gm. of sodium sulfadiazine per kilogram of body weight (1.2 and 1.7 Gm., equivalent to 7 Gm. in a man weighing 70 Kg.) was poured into the peritoneal cavity. The dogs recovered normally from the operation and remained well. The wounds healed without delay. Determinations of the level of drug in the blood and the urine showed (chart 2 *B*) that absorption was rapid but not more rapid than after intramuscular implantation and that good levels persisted for over twenty hours. Furthermore, the subsequent intraperitoneal implantation of a water-dispersible ointment containing 20 per cent sodium sulfadiazine (0.25 Gm. per kilogram of body weight) gave even more prolonged absorption. The blood level of sulfadiazine, for example, was 11 mg. per hundred cubic centimeters at five hours but was still 3 mg. per hundred cubic centimeters at sixty hours. Significant amounts of drug were excreted in the urine one or two days longer. In these two groups of experiments in dogs as well as in other experiments,<sup>8</sup> only 60 per cent of the drug implanted in the wound could be recovered in the urine. No explanation for this large deficit is yet available.

It is noteworthy that in these experiments the blood levels were similar to those found by Jorgenson<sup>11</sup> after the subcutaneous administration of sodium sulfadiazine in this dosage to infants. This suggests almost identical rates of absorption and excretion of sodium sulfadiazine whether administered subcutaneously, intramuscularly or intraperitoneally.

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19. When sodium sulfathiazole is used, a brownish discoloration of the dog's tissues occurs promptly. This does not occur with sodium sulfadiazine since this sodium salt is readily buffered within the physiologic  $p_H$  range.

20. All specimens of urine were examined when voided for drug crystals,  $p_H$  and drug concentration. No crystals were found; all specimens of urine were alkaline, their  $p_H$  being 8.0 or higher.

## COMMENT

These experiments in some measure establish the rationale of local chemotherapy by throwing light on the transport of sulfadiazine when a soluble nonirritating sulfonamide compound is applied locally. It is apparent that oral administration of sulfadiazine or the local use of sodium sulfadiazine in the rectus muscle, in the peritoneal cavity and by clysis under the skin all give similar blood levels. In other words, a given quantity of drug suitably administered by any of these routes is distributed similarly throughout the body. Presumably, then, the major advantages of this type of local therapy are as follows: In the involved local area a high concentration of drug is obtained immediately. In this area the concentration of drug is sustained over a period of twenty-four to forty-eight or more hours while the implanted drug is being transferred continuously but *completely* from the limited local area into the general circulation. As a result, the maximum blood level is attained relatively gradually and subsequently declines slowly. This is in sharp contrast to intravenous injection, which gives the undesirably high maximum blood level almost at once, followed by a rapid decline within two or three hours. Since the implanted drug is removed completely when a soluble derivative is used, foreign body reaction at the local site does not occur.

From these physicochemical measurements and from the preliminary animal experiments certain practical suggestions may be advanced. In the first place, the drawbacks encountered in the local use of sulfathiazole and sulfadiazine which result from their poor solubility may be circumvented by using their soluble sodium salts. The animal experiments prove them (particularly sulfadiazine) to be innocuous and nonirritating to tissues in relatively large doses, but the results of clinical studies now in progress <sup>20a</sup> must be evaluated before it is possible to decide finally on the usefulness of these salts in surgical procedures.

Another practical point is the observation that sulfathiazole and sulfadiazine are extensively ionized at the  $p_H$  of the blood and that when they are ionized their solubility is vastly increased over their solubility in water or any of the more common solvents, e. g. oils. This suggests that fluid or semifluid preparations, including ointments, should be prepared from the sodium salts in aqueous and not oily bases if high local drug concentrations are desired. For example, in preliminary clinical trials, 5 per cent sodium sulfadiazine in a glycerite of starch

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20a. Since this paper was submitted, sodium sulfadiazine powder has been tried clinically. After repeated direct application no local irritation has been observed.

21. Mayo, C. W., and Miller, J. M.: Solution of Sulfanilamide in the Local Treatment of Wounds, Proc. Staff Meet., Mayo Clin. **15**:609 (Sept. 25) 1940. Herrell, W. E., and Brown, A. E.: Local Use of Sulfonamide Compounds in the Treatment of Infected Wounds, *ibid.* **15**:611 (Sept. 25) 1940.

base has shown no inhibition of healing while providing good absorption of the drug. Likewise, for irrigation <sup>21</sup> far more concentrated solutions may be obtained if the drugs are dissolved in suitable buffers instead of distilled water or if the sodium salts dissolved in water are used.

So far as renal excretion is concerned, the acetyl derivatives like the free drugs form soluble sodium salts. Accordingly it seems that safe renal excretion would be insured by favoring sulfonamide salt formation by keeping the urine alkaline. Complete data on this problem will be published elsewhere.<sup>8</sup>

#### SUMMARY

The far greater antibacterial potency of sulfathiazole and sulfadiazine has been amply demonstrated, but their use locally in surgical procedures has been hampered by side effects resulting from their relative insolubility.

Measurements of the acidity of the drugs (dissociation constants) show that sulfathiazole and sulfadiazine are about as acidic as carbonic acid and that in biologic fluids ( $p_H$  7.5) they exist chiefly in the ionized form. This accounts for the fact that their concentrations in biologic fluids may be many times greater than their solubility in water.

Preliminary trials were made of the local effects of the sodium salts on tissues together with the rate and the extent of absorption of sodium sulfadiazine after intramuscular and intraperitoneal implantation in dogs. The results showed that sodium sulfadiazine in high concentration caused negligible irritation to tissues. Following either intramuscular or intraperitoneal implantation, sodium sulfadiazine is continuously transferred from the site of implantation to the general circulation over periods of twenty-four to forty-eight or more hours. Sodium sulfathiazole, on the other hand, gave evidence of some tissue irritation.

The local application of the sodium salts of sulfathiazole and especially of sulfadiazine warrants clinical trial. This is now in progress.

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# TREATMENT OF LARGE GASTRIC ULCERS

## RÉSUMÉ OF A TEN YEAR STUDY

FREDERICK STEIGMANN, M.D.

CHICAGO

The correct treatment of large gastric ulcers is not generally agreed on. The question "Is every large gastric ulcer to be operated on?" has aroused much controversy in the past, and it is still disputed.

In this paper evidence is presented to show that every large gastric ulcer is a condition for operation. This conclusion is not based on the belief that every large gastric ulcer is or may turn into a carcinoma, although that is an important factor. The fact that only a small percentage of large gastric ulcers are malignant or may become malignant should not deter from surgical intervention. Neither the patient who has such a lesion nor the clinician who treats him can be at ease if only 5 per cent or less of such lesions are known to turn malignant.

The difficulty of accurately diagnosing whether a large gastric ulcer is benign or malignant has been stressed by numerous investigators and by me in recent publications.<sup>1</sup> It has been often stated that in spite of improvement in roentgen technic, the advent of gastroscopy and improvement in medical management there is still no definite criterion for an accurate diagnosis of large gastric ulcer. Studies in other clinics and at the Cook County Hospital definitely convince one that there are no reliable data obtainable from the history, the physical examination, the laboratory test, the roentgen and gastroscopic examinations or the clinical response to medical treatment which will assure one that a lesion is benign or malignant.

A comparatively high percentage of large gastric ulcers that prove to be benign have a history of only several months' duration, while, con-

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From the Cook County Hospital and the Department of Internal Medicine, the University of Illinois College of Medicine.

1. (a) Holman, C. W., and Sandusky, W. R.: Further Observations on the Diagnosis and Treatment of Gastric Lesions, *Ann. Surg.* **112**:339-343 (Sept.) 1940. (b) Allen, A. W., and Welch, C. E.: Gastric Ulcer: The Significance of This Diagnosis and Its Relationship to Cancer, *ibid.* **114**:498-506 (Oct.) 1941. (c) Freedman, E., and Goehring, H. D.: Diagnostic Errors in Ulcerative Lesions of the Stomach and Duodenum, *Am. J. Roentgenol.* **44**:48-58 (July) 1940. (d) Eusterman, G. B.: Carcinomatous Gastric Ulcer: Misleading Results of Medical Therapy, *J. A. M. A.* **118**:1-5 (Jan. 3) 1942. (e) Mass, M., and Steigmann, F.: Carcinoma in Clinically Benign Gastric Ulcer, *Illinois M. J.* **75**:120-122 (Feb.) 1939.

trariwise, many proved carcinomatous ulcers have a history of gastric disturbances for years (fig. 1). Secondly, some patients with benign gastric ulcers are cachectic, while some with malignant lesions of the stomach present little external appearance of having malignant growths. Thirdly, in contradistinction to what occurs with duodenal ulcer, achlorhydria is not uncommon in patients with gastric ulcer, while a goodly number of patients with a carcinomatous ulcer may have free acid values above 40 degrees (fig. 2). Furthermore, in cases in which there is a large gastric niche the roentgen diagnosis is usually a presumptive one, since nearly all the criteria which differentiate benign from malignant lesions are distorted (fig. 3). Comparison of the roentgen and

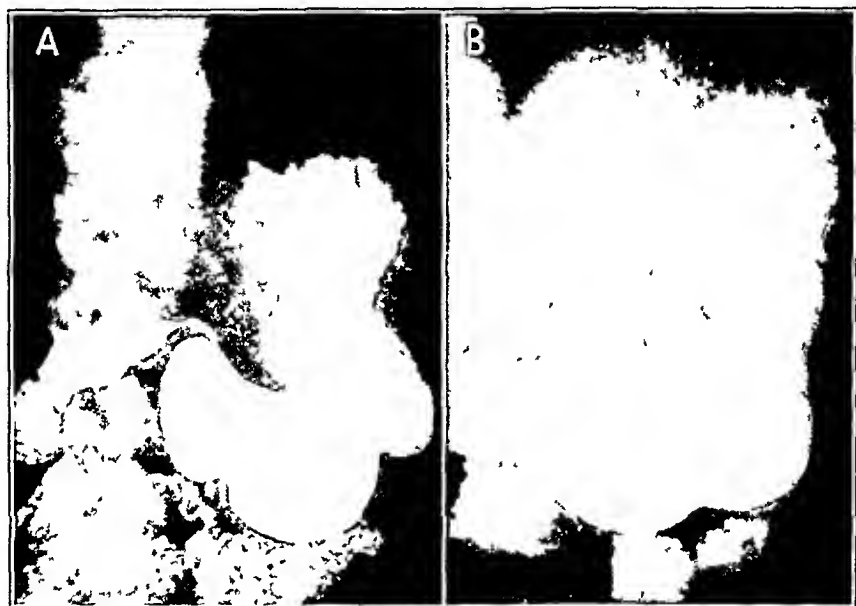


Fig. 1.—*A*, roentgenogram of an ulcer with a history of short duration (three months) diagnosed as benign on histologic examination. It was diagnosed as malignant clinically, chemically, roentgenologically, gastroscopically and at operation. *B*, roentgenogram of an ulcer with a twelve year history simulating peptic ulcer. It was diagnosed as malignant on histologic examination. It was diagnosed as benign clinically, chemically and gastroscopically and improved when the patient was subjected to a medical regimen.

histologic reports on such lesions proves the roentgenologist correct in much less than 90 per cent of the cases. Roentgen examination is not the only means which fares badly in the diagnosis of large gastric ulcers; gastroscopy does little better. I have seen instances of a malignant ulcer being called benign and vice versa (fig. 4). Lastly, benign ulcers will often respond poorly to medical treatment, while malignant ulcers may



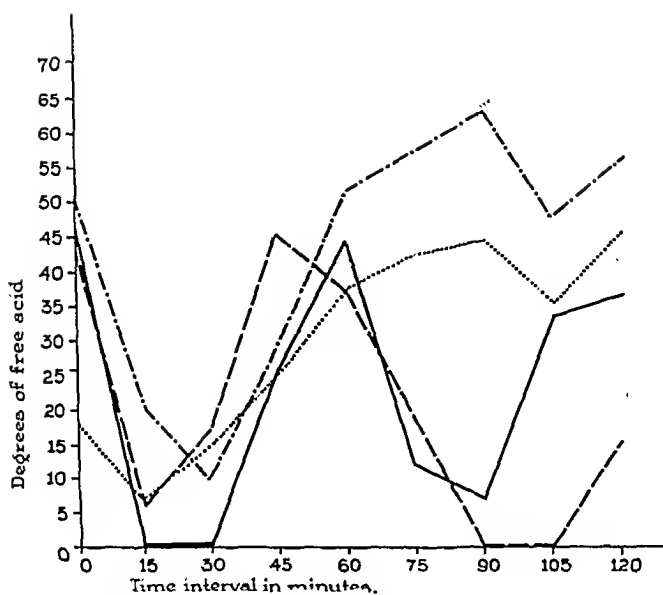


Fig. 2.—Graph showing several acidity curves for a patient with a large ulcerating gastric carcinoma in the pars angularis. The dotted line represents the control curve; the broken line represents the curve for karaya; the solid line, the curve for colloidal suspension of aluminum hydroxide, and the dot and dash line, the curve for acid B, a preparation of dilute nitric acid, bismuth subcarbonate and water.

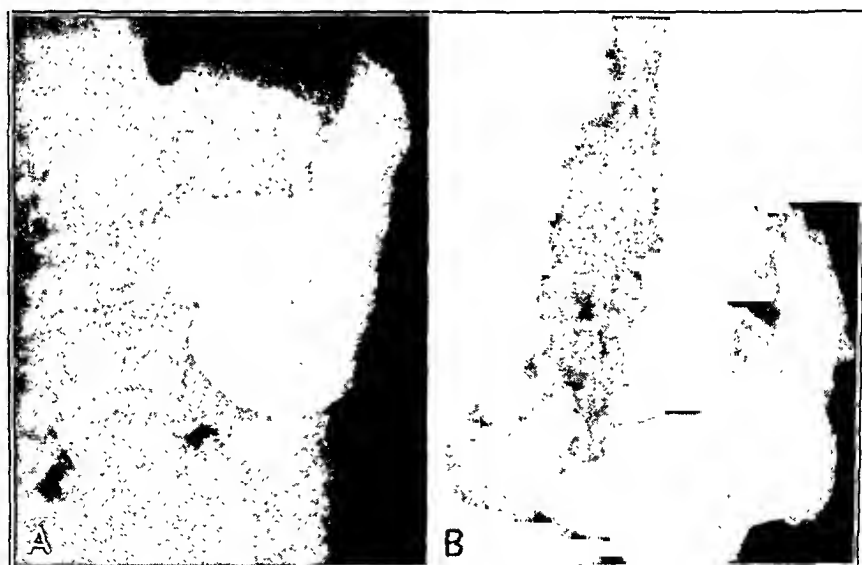


Fig. 3.—*A*, roentgenogram of an ulcer with a short history diagnosed histologically as benign but clinically and roentgenologically as malignant. *B*, roentgenogram of an ulcer with a short history diagnosed histologically as benign and roentgenologically and gastroscopically as malignant.

show a remarkable response to medical treatment and thus give both patient and doctor a false sense of security<sup>1a</sup> (fig. 5).

The surgeon, looking at the exposed lesion, is in many instances unable to tell whether an ulcer is benign or malignant. The pathologist will often fail to tell from the gross appearance of an ulcer whether it is benign or malignant. Only by careful histologic examination of various parts (floor, walls and margins) of an ulcer can one accurately decide on the character of the lesion (fig. 6). The histologic examination of various parts is stressed because frequently one part of the lesion may have a benign appearance while the other parts show signs of malignancy. From these remarks, it is obvious that for a correct



Fig. 4.—*A*, roentgenogram of an ulcer called malignant after histologic examination but benign after gastroscopic examination. *B*, roentgenogram of an ulcer called benign after histologic examination but malignant after gastroscopic examination.

diagnosis of large gastric ulcer histologic examination is imperative, and this entails resection.

Assuming that a large gastric ulcer is benign, one still must ask oneself "Should it be treated medically?" From observations during the past ten years of a large number of patients with large ulcers, it is my opinion that in the majority of cases not much is gained by medical management and that frequently the patient is better off if his lesion is resected as soon as diagnosed, because usually after years of medical management he is finally subjected to surgical intervention.

Owing to ignorance of the causation of peptic ulcer, both gastric and duodenal ulcers are called and treated as peptic ulcers. In reality,

however, the two are different. They differ as to age groups, gastric acidity, complications and treatment. However, there may be as much difference between a large and a small gastric ulcer as between a gastric and a duodenal ulcer. Therefore, it should be emphasized that this paper deals particularly with large gastric ulcers. A large gastric ulcer differs from a small one in the history, the physical examination, the laboratory findings, the roentgen and gastroscopic observations and the response to medical treatment.

With these things in mind, routine surgical intervention is not advocated for all gastric ulcers but for the large ones only. When any ulcer responds poorly to medical treatment, it is presumptive evi-



Fig. 5.—Roentgenogram of an ulcer niche diagnosed as malignant histologically and decreasing to less than one fourth its original size on medical management.

dence that it is malignant. It is certainly not a benign condition which keeps the patient in a chronically ill state, which makes him a chronic invalid and which ultimately sends him to operation for relief of the symptoms. These statements are based on the observation of the life cycle of large gastric lesions. To repeat, even if it is assumed such a lesion is benign, long resistance to treatment, with the probability of complications, indicates operation rather than procrastination with medical management and operation only as a last resort.

It is not within the scope of this paper to give in detail the various complications which may arise from large gastric ulcers, complications

which make them malignant in spite of being histologically benign. I shall mention some of the complications, however, to illustrate the basis for my views.

#### NONHEALING

It is known that most large gastric ulcers heal poorly under medical management, in spite of the fact that some have apparently healed. I have seen a number of such apparently healed ulcers. Nevertheless, the percentage of relapses is so large that the treatment cannot be considered ideal. It is discouraging to both the doctor and the patient when



Fig. 6.—Roentgenogram of a large ulcer showing malignant changes on its margin.

a lesion that remains small for months or disappears entirely suddenly develops into a large ulcer.<sup>2</sup> In many instances, medical regimen and even palliative gastroenterostomy do not prevent the ulcer from getting larger and penetrating into the neighboring viscera (fig. 7). Jordan<sup>3</sup>

2. Palmer, W. L.; Schindler, R., and Templeton, F. C.: The Development and Healing of Gastric Ulcer: A Clinical Gastroscopic and Roentgenologic Study, *Am. J. Digest. Dis.* **5**:501-522 (Oct.) 1938.

3. Jordan, S. M.: The Problems of Peptic Ulcer, *S. Clin. North America* **21**:665-677 (June) 1941.

expressed the opinion that such a nonhealing lesion indicates operation. It keeps the patient in a chronic state of invalidism until resection relieves him.

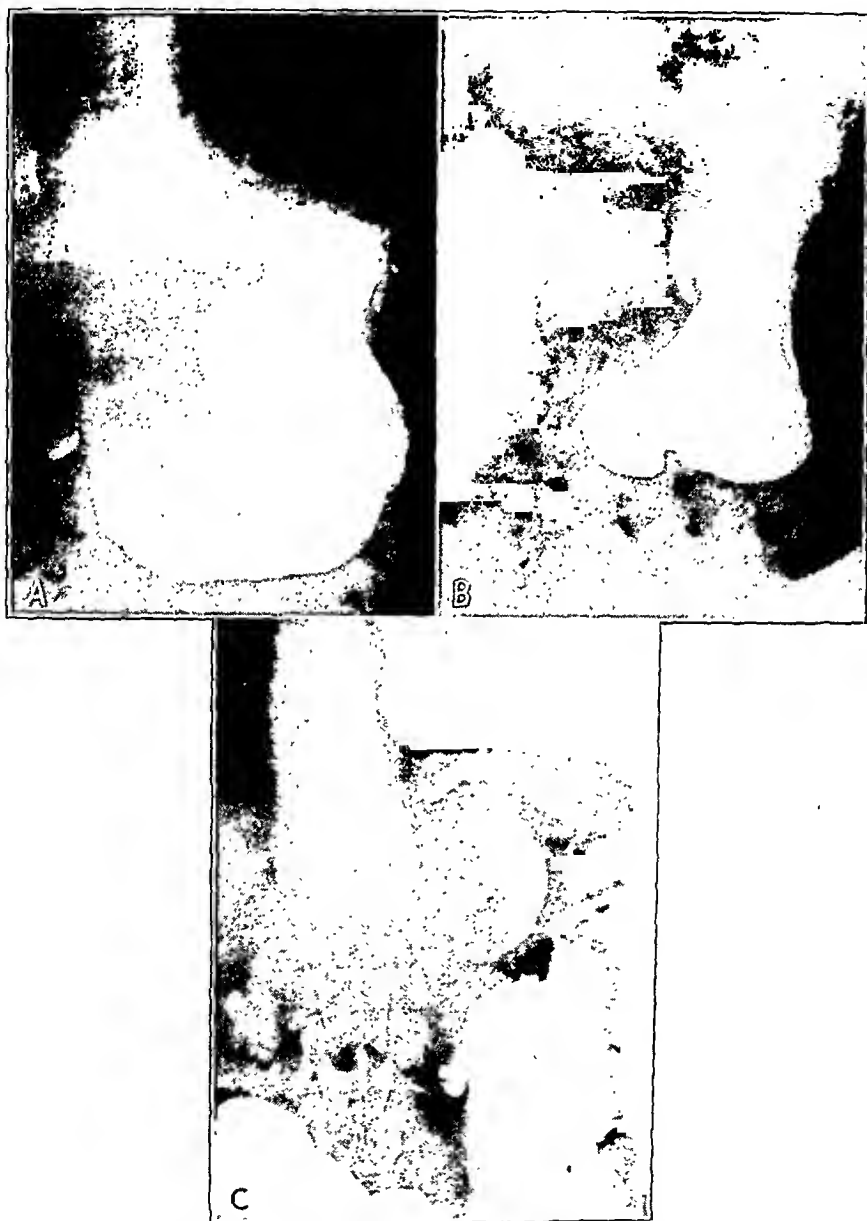


Fig. 7.—Roentgenograms (*A*) of a large benign ulcer which perforated, (*B*) of the same ulcer three months after medical treatment and (*C*) of the same ulcer five years later. In the interim between *B* and *C* the patient underwent gastroenterostomy.

#### BLEEDING

Hemorrhage from a gastric ulcer is a serious omen at any time. The seriousness, however, is much graver when bleeding occurs from a

large gastric ulcer. The mortality rate associated with bleeding ulcers, both gastric and duodenal, varies in different clinics from 3 to 33 per cent.<sup>4</sup> In this hospital it is around 8 per cent on the average with all types of treatment. However, the mortality from large bleeding gastric ulcers is close to 50 per cent. The reason for this is, of course, obvious, in that the bleeding occurs in an elderly person who has sclerotic vessels which cannot be expected to contract spontaneously. Furthermore, these vessels are usually embedded in cicatricial tissue, which likewise prevents spontaneous contraction of the vessel (fig. 8). Patients with

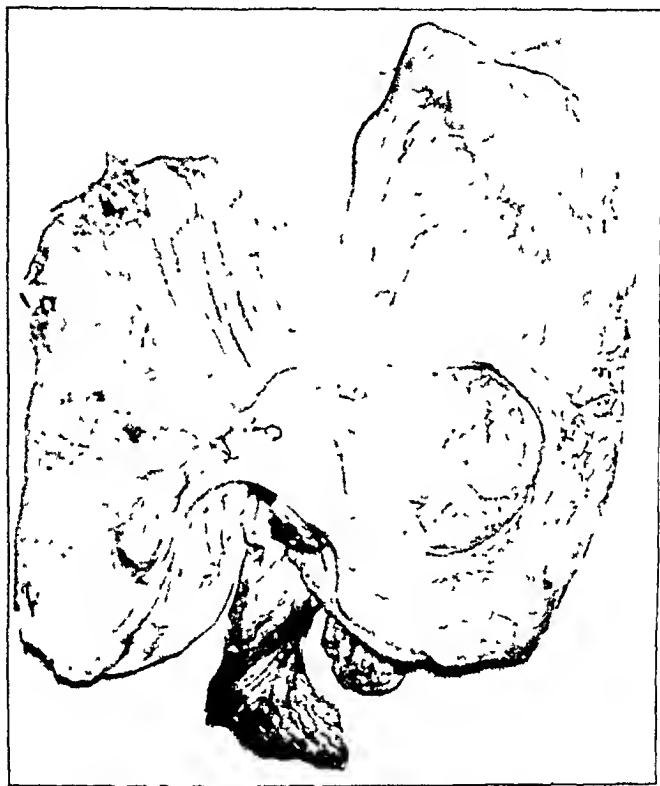


Fig. 8—Photograph of a large benign ulcer showing gaping blood vessels which led to the patient's death from massive hemorrhage.

such a condition, therefore, present immediate operative emergencies when bleeding occurs. It is clear, moreover, that an elective operation on a large gastric ulcer with careful preoperative preparation is preferred to an emergency operation when bleeding occurs.

4. Allen, A. W.: Acute Massive Hemorrhage from the Upper Gastrointestinal Tract with Special Reference to Peptic Ulcer, *Surgery* **2**:713-731 (Nov.) 1937. Allen, A. W., and Benedict, E. B.: Acute Massive Hemorrhage from Duodenal Ulcer, *Ann. Surg.* **98**:736-749 (Oct.) 1933. Blackford, J. M., and Cole, W. S.: Massive Hemorrhage from Peptic Ulcer, *Am. J. Digest. Dis.* **6**:637-641 (Nov.) 1939. Blackford, J. M., and Williams, R. H.: Fatal Hemorrhage from Peptic Ulcer, *J. A. M. A.* **115**:1774-1776 (Nov. 23) 1940.

## PERFORATION AND PENETRATION

Perforation into the abdominal cavity and penetration into an adjacent organ occur frequently from a large gastric ulcer. Perforation of a large gastric ulcer, while not more frequent than that of any other ulcer, is more serious because the large hole permits more widespread infection. Penetration, however, is a much more common occurrence and actually represents a perforation of the ulcer into the neighboring viscera—the pancreas, the liver and the small peritoneal cavity. At times, spontaneous perforation into the duodenum, the jejunum or the colon occurs.<sup>5</sup> Such penetration leads to formation of adhesions and inflammatory granuloma between the stomach and the particular organs,

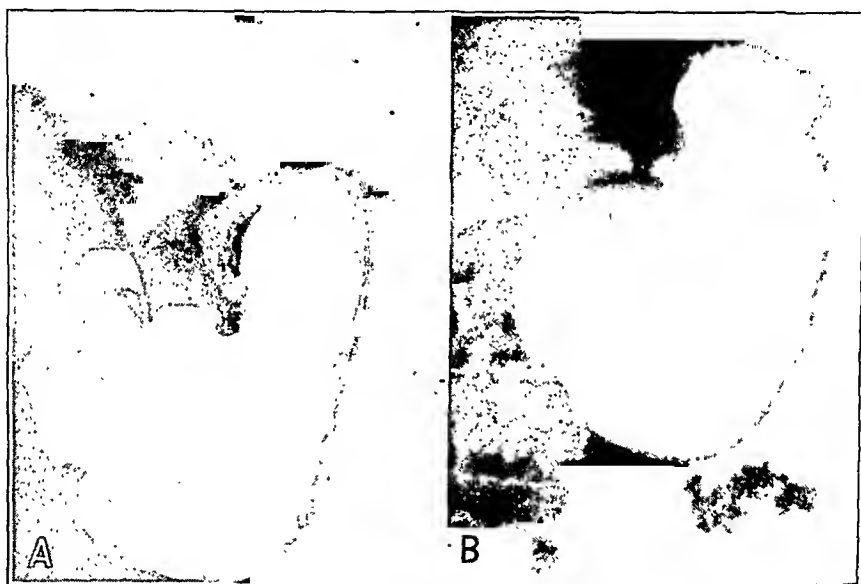


Fig. 9.—*A*, roentgenogram of a large benign ulcer causing tobacco pouch stomach. Note the narrow pylorus close to the base of the gastric ulcer. *B*, roentgenogram of a large benign ulcer causing tobacco pouch stomach.

which in turn produce anatomic deformities that interfere with the motor functions of the stomach and are frequently responsible for many of the so-called intractable ulcer symptoms. Removal of the large gastric ulcer at an early stage would prevent some of these complications.

5. Steigmann, F., and Bach, A. C.: Peptic Ulcer and Gastroduodenal Fistulae, *Am. J. Surg.* **52**:355-359 (May) 1941. Henke, F., and Lubarsch, O.: Verdauungsslauch, in *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 4, pt. 1. Casellas, R. R.: An Unusual Pathologic Condition of the Stomach with Abnormal Opening into the Jejunum, *J. A. M. A.* **87**:1393 (Oct. 23) 1926. Monroe, R. T.: Fistula as a Complication of Peptic Ulcer, *Am. J. M. Sc.* **174**:599-609 (Nov.) 1927.

## TOBACCO POUCH STOMACH

The so-called tobacco pouch stomach may produce symptoms and signs resembling those of penetration. The tobacco pouch stomach is one produced by shrinking of the scar tissue of a healed large gastric ulcer with ensuing traction on the duodenal cap leading to shortening and rolling in like a snail<sup>6</sup> of the lesser gastric curvature (fig. 9). This deformity takes years to develop, during which time the patient has various symptoms, and finally it produces symptoms of obstruction which invariably require operation for their relief.

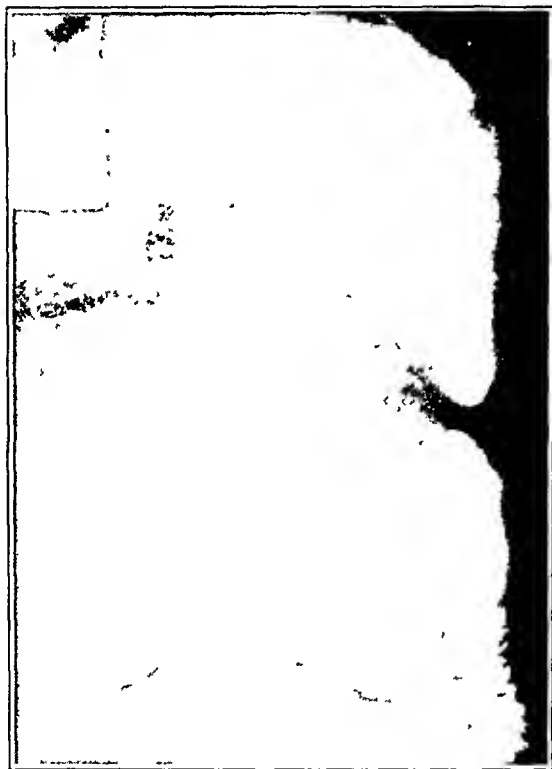


Fig. 10.—Persistent cicatricial hourglass deformity following a large gastric ulcer.

## HOURLASS STOMACH

Severe hourglass deformity following a large gastric ulcer (fig. 10) is the least common complication; I found it in about 4 per cent of the cases in my series. Since it requires surgical intervention and this

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6. Ludin, M.: Beiträge zur Magenröntgenologie, Arch. f. Verdauungskr. **32**: 299-312, 1924. Melchart, F.: Zur Frage der Fistula gastroduodenalis im Röntgenbilde, Fortschr. a. d. Geb. d. Röntgenstrahlen **44**:335-342, 1931. Low-Beer, A.: Fistula gastroduodenalis im Röntgenbilde, *ibid.* **43**:435-441, 1931.



usually on a debilitated patient with symptoms of chronic obstruction, it presents additional proof against the prolonged medical treatment of large gastric ulcers.

#### CARCINOMATOUS DEGENERATION

The possibility that a gastric ulcer may become malignant has been controverted for many years. Without alining myself with those who believe in such a possibility<sup>7</sup> or with those who stanchly deny it,<sup>8</sup> I may say that I have encountered 3 cases in which a gastric ulcer apparently became carcinomatous. One of the ulcers presented both benign and carcinomatous characteristics in the histologic section. In spite of the fact that my percentage of malignant transformation of gastric ulcers is low, it must be emphasized that this low percentage cannot be used as support of the nonintervention idea for the treatment of large gastric ulcers, since no one can tell definitely or with assurance where this 1 or 2 per cent incidence will fall.

Without presuming to tell surgeons what to do, I may state that in my series of cases high gastrectomy with few exceptions was the procedure of choice in the surgical treatment of large gastric ulcers. Only a few patients had less radical procedure, mainly because anatomic changes and infectious granuloma and cicatricial contraction of these large gastric ulcers prevented or made it unwise surgically to remove two thirds or four fifths of the stomach. All patients had careful pre-operative preparation for four to six days, with attention paid especially to their state of hydration, vitamin, mineral and acid-base balance and blood picture. Blood transfusions were given in most instances before and after operation as required. Postoperatively a modified regimen suggested by McNealy<sup>9</sup> was followed. In recent years spinal anesthesia has been the one of choice in these operations. Last but not least, most of the operations were done by men particularly trained and apt in gastric procedures.

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7. Scott, W. J. M., and Mider, G. B.: Malignancy in the Chronic Gastric Ulcer, *Am. J. Surg.* **40**:47-50 (April) 1938. Bloomfield, A. L.: The Diagnosis of Early Cancerous Changes in Peptic Ulcer, *J. A. M. A.* **104**:1197-1201 (April 6) 1935. Wilensky, A. O., and Thalheimer, W.: Etiological Relationship of Benign Ulcer to Carcinoma of the Stomach, *Ann. Surg.* **67**:215-225 (Feb.) 1918.

8. Palmer, W. L.: Benign and Malignant Gastric Ulcers: Their Relation and Clinical Differentiation, *Ann. Int. Med.* **13**:317-338 (Aug.) 1939. Ewing, J.: Relation of Gastric Ulcer to Cancer, *Ann. Surg.* **67**:715-724 (June) 1918; Beginnings of Gastric Cancer, *Am. J. Surg.* **31**:204-205 (Feb.) 1936. Klein, S. H.: Origin of Carcinoma in Chronic Gastric Ulcer, *Arch. Surg.* **37**:155-174 (July) 1938.

9. McNealy, R. W.: Preoperative and Post-Operative Management of Gall Bladder Disease, *J. Kansas M. Soc.* **41**:497-502 (Dec.) 1940.

## SUMMARY AND CONCLUSIONS

Studies and observations of over 200 patients with large gastric ulcers during a period of ten years lead me to believe that surgical intervention is the treatment of choice, in spite of the fact that many may do well on a medical regimen. This belief is based on the following facts: 1. In most cases of large gastric lesions, a definite diagnosis between benign and malignant cannot be made. 2. Even if benign large ulcers often produce chronic invalidism, they heal poorly, bleed dangerously and even in healing may lead to various complications which ultimately require operation as an emergency measure on debilitated ill patients. 3. Considering the uncertainty of diagnosing such ulcers correctly, their poor and uncertain healing and frequent remissions, their serious complications, even if benign, and their possible although rare malignant degeneration, it seems logical to recommend operation at an early stage.

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# RELATION OF SERUM PROTEIN TO WELL HEALED AND TO DISRUPTED WOUNDS

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AND

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In a previous paper<sup>1</sup> we reported observations on the relation of serum protein concentration to wound healing in human beings. The study consisted of details regarding the total protein, albumin and globulin, the albumin-globulin ratio and the calculated protein oncotic pressure of the serum of patients in the postoperative state whose wounds had been carefully observed. These patients fell into three groups, namely, those with clean wounds (hernial and laparotomy), those with deeply infected wounds (below the deep fascia) and those with disrupted wounds. It was concluded that in general patients who had deep infection or disruption of their wounds showed lower values for total protein and for oncotic pressure in their serum. This was due mainly to a diminution in the albumin fraction.

In this paper we shall present additional data regarding the relation of serum protein concentration to clean wounds and disrupted wounds. We shall also present data on total proteins in 1,358 consecutive admissions to our surgical service.

The relation of serum protein concentration to wound healing was studied in 80 patients. Forty had clean well healed wounds, and 40 had disruptions. In 17 of the patients with clean wounds (hernioplasties) the determinations were done from one to ten days after operation (average, four days). In the other 23 (clean laparotomy wounds) the determinations were done from one to twenty-two days postoperatively (average, eight days). In 1 case of disruption the determinations were made four days before rupture, and in the other 39 cases of disruption the determinations were made on the day of rupture or the following day.

The values for total serum protein were determined by aeration and titration after micro-Kjeldahl digestion.<sup>1a</sup> The values for albumin were determined after precipitation of globulin with sodium sulfate.

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From the Crown Heights Hospital.

1. Koster, H., and Shapiro, A.: Serum Proteins and Wound Healing, *Arch. Surg.* **41**:723 (Sept.) 1940.

1a. Sobel, A. E.; Yuska, H., and Cohen, J.: Convenient Method of Determining Small Amounts of Ammonia and Other Bases by the Use of Boric Acid, *J. Biol. Chem.* **118**:443, 1937.

All patients were operated on under spinal anesthesia. Their ages ranged from 18 to 77 years. The average age in the group with clean wounds was 36.5 years. The average age in the group with disrupted wounds was 49.7 years. Sixty-eight per cent of the patients in the group with disrupted wounds had operations for lesions of the duodenum or the stomach or for cancer of some part of the gastrointestinal canal.

All laparotomy wounds were sutured in three layers, continuous plain catgut no. 2 being used for the peritoneum, continuous twenty day chromic catgut no. 2 for the fascia and continuous black silk for the skin. In the hernioplasty wounds the internal oblique muscle and the conjoined tendon (Bassini) or the internal oblique muscle, the conjoined tendon and the external oblique aponeurosis (Ferguson-Andrews) were sutured to the inguinal ligament with interrupted twenty day no. 2 chromic catgut. The skin was closed by continuous black silk suture.

The results are summarized in tables 1 and 2.

It can be seen from the tables that the average values for total protein and the albumin fractions were lower in the patients with disrupted wounds than in the patients with normal wounds. In the patients with disrupted wounds the mean value for total protein was 6.19; the standard deviation, 0.62, and the standard error, 0.102. In the patients with normal wounds the mean value was 6.76; the standard deviation, 1.55 and the standard error, 0.245. That the difference between the means of the patients with disrupted and those with well healed wounds is significant can be seen by applying the formulas:

$$\sigma = \sqrt{S.E._1^2 + S.E._2^2} \text{ and } P = \frac{X}{\sigma},$$

in which  $\sigma$  is the standard deviation of the theoretic distribution of the difference between the means; S. E. is the standard error; P is the probability of the difference being accidental, and X is the numerical difference between the observed means. The result of such a calculation yields a probability of 3.16 chances in 100 of the difference between the means of the patients with disrupted and those with well healed wounds occurring accidentally; this difference of course is significant.

The mean value for albumin in the patients with disrupted wounds was 3.26; the standard deviation, 0.45, and the standard error, 0.07. The mean value in the patients with well healed control wounds was 4.21; the standard deviation, 1.38, and the standard error, 0.22. The calculation of significance of the difference between the albumin mean values in the patients with disrupted and those with normal wounds according to the formulas already given yields a probability of less than 1 chance in 10,000 that such difference could occur accidentally. This confirms our previously reported observation<sup>1</sup> that the fall in total proteins found in patients with disrupted wounds is due entirely to the

loss of albumin and suggests strongly that a more accurate picture of protein disturbance can be obtained if besides total protein the albumin fraction is also determined.

In an earlier report we presented data on serum protein concentration in 7 cases of wound disruption; these data are incorporated in this paper. Subsequently, Hartzell and associates<sup>2</sup> reported the serum

TABLE 1.—*Values for Serum Protein, Serum Albumin and Serum Globulin in Forty Patients with Clean Operative Wounds*

Days Between Operation and Determination	Protein (Gm. per 100 Cc. Serum)	Albumin (Gm. per 100 Cc. Serum)	Globulin (Gm. per 100 Cc. Serum)
7.....	5.46	3.52	1.94
2.....	5.64	4.56	1.08
2.....	5.74	4.38	1.36
22.....	5.75	2.82	2.93
8.....	5.87	3.64	2.23
2.....	5.88	3.46	2.42
3.....	5.95	4.21	1.74
1.....	5.95	3.84	2.11
12.....	6.01	3.69	2.32
9.....	6.05	3.85	2.20
8.....	6.09	3.84	2.25
1.....	6.15	4.58	1.57
5.....	6.17	4.05	2.12
7.....	6.20	3.90	2.30
14.....	6.38	4.61	1.77
10.....	6.53	4.33	2.20
9.....	6.59	4.74	1.85
5.....	6.60	3.18	3.42
19.....	6.69	4.12	2.57
11.....	6.72	4.19	2.53
6.....	6.72	4.12	2.60
10.....	6.74	4.58	2.16
2.....	6.75	4.42	2.33
9.....	6.75	3.46	3.29
3.....	6.85	4.69	2.16
2.....	6.88	4.65	2.23
7.....	7.06	3.76	3.30
10.....	7.13	3.90	3.23
4.....	7.25	4.89	2.36
1.....	7.40	4.02	3.38
11.....	7.51	4.04	3.47
5.....	7.57	4.77	2.80
10.....	7.60	3.54	4.06
2.....	7.68	4.39	3.29
2.....	7.75	4.76	2.99
1.....	7.82	5.13	2.69
8.....	7.88	4.62	3.26
3.....	7.90	5.24	2.66
1.....	8.30	5.23	2.97
2.....	8.40	5.53	2.87
Mean value.....	6.76	4.21	
Standard deviation.....	1.55	1.38	
Standard error.....	0.245	0.22	

protein concentration in 20 cases of wound disruption to be uniformly below normal values. Using their data and calculating the significance of the difference between their mean values and the mean values found in our cases of well healed wounds as normal, we found further con-

2. Hartzell, J. B.; Winfield, J. M., and Irvin, J. L.: Plasma Vitamin C and Serum Protein Levels in Wound Disruption, J. A. M. A. **116**:669 (Feb. 22) 1941.

firmation that protein disturbance in wound disruption is more evident in the albumin fraction.

The serum protein values in our cases of disruption were not uniformly low. In 11, or 28 per cent, of the 40 cases there were values which ranged from 6.50 to 7.31, averaging 6.94. These are well within normal limits. In 23, or 58 per cent, there were values above 6.0. On the other hand there were 15 cases, or 38 per cent, of the 40 cases of

TABLE 2.—*Values for Serum Protein, Serum Albumin and Serum Globulin in Forty Patients with Disrupted Operative Wounds*

Days from Operation to Disruption	Protein (Gm. per 100 Cc. Serum)	Albumin (Gm. per 100 Cc. Serum)	Globulin (Gm. per 100 Cc. Serum)
10.....	4.32	2.88	1.44
6.....	4.50	2.00	2.50
17.....	5.01	2.80	2.24
8.....	5.25	3.33	1.92
10.....	5.51	2.60	2.91
8.....	5.72	3.39	2.33
6.....	5.73	3.37	2.36
9.....	5.74	3.86	1.88
12.....	5.77	3.24	2.53
0.....	5.82	2.84	2.98
7.....	5.86	3.23	2.63
3.....	5.86	2.90	2.96
8.....	5.87	2.24	3.63
8.....	5.91	3.16	2.75
9.....	5.92	3.64	2.28
7.....	5.94	3.20	2.74
8.....	5.96	3.62	2.34
3.....	6.04	3.04	3.00
13.....	6.04	3.04	3.00
12.....	6.05	3.09	2.96
6.....	6.05	3.09	2.96
9.....	6.08	3.07	3.01
6.....	6.12	3.06	3.06
15.....	6.14	3.09	3.05
8.....	6.18	3.07	3.11
9.....	6.25	3.74	2.51
4.....	6.30	4.22	2.08
13.....	6.38	3.80	2.58
10.....	6.38	3.80	2.58
6.....	6.70	2.93	3.72
7.....	6.70	2.98	3.72
9.....	6.71	3.61	3.10
16.....	6.81	3.72	3.09
5.....	6.86	3.81	3.05
8.....	6.86	3.06	3.20
7.....	6.96	3.81	3.15
5.....	7.12	3.47	3.65
8.....	7.16	3.54	3.62
5.....	7.17	3.60	3.57
8.....	7.31	3.92	3.39
Mean value.....	6.19	3.26	
Standard deviation.....	0.62	0.45	
Standard error.....	0.102	0.07	

clean abdominal wounds in which total protein values were less than 6.50, ranging as low as 5.46.

Similarly in 7, or 18 per cent, of the 40 cases of disruption there were albumin values of more than 3.75 Gm. per hundred cubic centimeters, whereas in 8, or 20 per cent, of the 40 cases of clean wounds there were values of 3.75 or less.

Among the 20 cases studied by Hartzell and associates<sup>2</sup> there were only 5 cases in which there was a total protein concentration greater

than 6.0, whereas we had 11 cases of disruption in which there were values above 6.5. Because of the small number of cases this difference need not be significant.

There is a great likelihood that the protein values in our well healed cases are low. The table of normal values for serum protein and the albumin fraction representing 9 different groups of observations collected by Muntwyler<sup>3</sup> shows a 7 per cent value for total protein and a 4.6 per cent value for albumin. These values cannot be used for comparison because the complete data are lacking and standard deviations thus cannot be calculated.

The literature regarding serum protein values is not satisfactory. Some time after the study of serum protein relation to disruption had been started, we decided to obtain our own data, and we did determinations on patients in a consecutive series of 1,358 hospital admissions to our surgical service. In these cases total proteins were calculated by the specific gravity method.<sup>4</sup> We found an average value of 6.88 Gm. per hundred cubic centimeters. The range was between 4.9 and 8.2; the standard deviation was 0.173, and the standard error was 0.0047 (see chart).

If these data are used as representative of an average normal for comparison with the values of total protein in our cases of disrupted wounds, the difference is statistically highly significant.

In this series of 1,358 cases of routine serum protein concentration observations there were 4 cases of wound disruption, an incidence of 0.29 per cent. (This is in close agreement with our previously reported findings<sup>5</sup> of 17 disruptions in 7,892 laparotomies, an incidence of 0.22 per cent.) These 4 cases of disruption had serum protein concentrations ranging from 6.3 to 7.3. As can be seen from the distribution curve, there were 87 cases in the series in which the protein concentration ranged from 4.8 to 6.0, and in none of these did disruption occur. This seems to emphasize the previously expressed opinion that the occurrence of normal concentration of serum protein and albumin in some patients whose abdominal wounds have disrupted and of relatively low concentrations in many with clean wounds means that hypoproteinemia by itself is neither a necessary nor a sufficient condition for the development of wound disruption.

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3. Muntwyler, C.: Plasma Proteins, in Piersol, G. M., and Bortz, E. L.: *The Cyclopedia of Medicine*, Philadelphia, F. A. Davis Company, 1932, vol. 6, p. 430.

4. Barbour, H. G., and Hamilton, W. F.: Blood Specific Gravity: Its Significance and a New Method for Its Determination, *Am. J. Physiol.* **69**:654, 1924.

5. Koster, H., and Kasman, L. P.: Wound Disruption, *Am. J. Surg.* **31**: 537, 1936.

A most striking example is found in a recent case not included in the groups presented in the tables.

#### REPORT OF A CASE

J. K., a white man 26 years of age, a clerk by occupation, was admitted to the hospital on Dec. 29, 1941. He complained of sudden sharp severe cramplike pains across the middle of the abdomen three years previously; these had gradually subsided in three days. There was no accompanying nausea, vomiting, fever, anorexia, distention or diarrhea. He was well for one year, and then he had another milder attack which subsided in three days. Eight months later there was a third attack and eight months after that a fourth attack. Two years

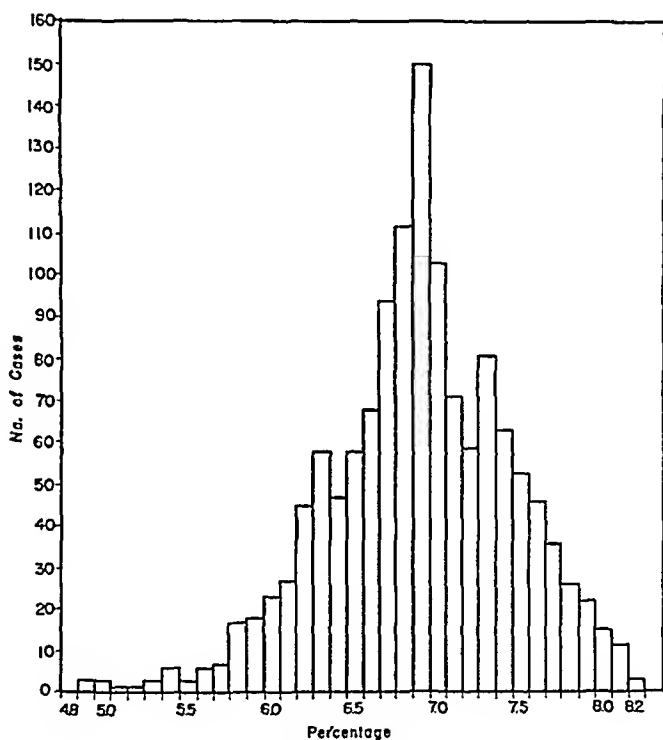


Chart showing frequency distribution curve of total serum protein values in 1,358 patients on whom operation was performed.

before admission his bowel habit gradually changed from two formed stools daily to three or four stools daily of semisolid and sometimes watery consistency. This semidiarrhea would last one to three days, and then the stool would become more solid. These stools were not accompanied by any cramps or pain. During the last year before admission the diarrhea (which became worse) was associated with borborygmus, and the patient himself noticed peristalsis on the abdominal wall. Three months before admission swelling of the legs, the thighs and the scrotum developed, and he had abdominal cramps constantly. For the last few weeks before admission the diarrhea was almost constant, and the stools were foamy, and he had dyspnea on walking. He lost 37 pounds (16.8 Kg.) in the last fifteen months.



The patient related a previous history of asthma at the age of 10 and bronchitis which was relieved after a series of treatments with vaccine. He underwent tonsillectomy fourteen years before admission.

Physical examination revealed pallor of the face and emaciation of the body with edema of both lower extremities, the scrotum and the penis and a large distended abdomen with visible peristalsis. There were numerous coarse and sonorous rales over both lung fields. The heart sounds were of good quality with no murmurs. The abdomen was not tender. There were no palpable masses, but borborygmus was evident. There was a fluid wave in the abdomen, and there was pitting edema of the thighs and the legs. The blood pressure was 102 systolic and 64 diastolic. Roentgen examination showed a normal chest. Electrocardiographic examination revealed no abnormalities. A gastrointestinal roentgenogram showed the entire ileum distended as a result of an obstruction at the ileocecal junction. An enema of barium sulfate also showed the ileocecal obstruction. The hemoglobin was 64 per cent. The red blood cell count was 3,260,000. The white blood cell count was 10,400. The differential count showed 76 per cent polymorphonuclear leukocytes, 21 per cent lymphocytes and 3 per cent mononuclear cells. The urine was normal. The Kahn test gave negative results. The sedimentation time was normal. Blood chloride, calcium and urea nitrogen were all normal. The total protein was 4.6; the albumin, 1.8; the globulin, 2.8. The glucose tolerance test gave normal values. The stool showed no evidence of dysentery, bacillary and amebic. The basal metabolic rate was -20 per cent. The Rehfuess test meal showed normal gastric secretion. There was no blood in the stool.

The absence of significant cardiac or renal involvement suggested that the edema was of nutritional origin as a result of a low grade intestinal obstruction accompanied by defective absorption and assimilation from the small intestine. The obstruction was believed to be due to terminal ileitis. The patient was prepared for operation by a diet high in protein and vitamins, including mineral salts, and blood transfusions. One cubic centimeter of mercupurin given intramuscularly on the day after admission at 1:30 p. m. was followed by an output of 142 oz. (4,199 cc.) of urine within six hours with an intake of only 18 oz. (532 cc.) of water. In the subsequent twelve hours 900 cc. more urine was eliminated, and the edema was practically gone the following morning. Three days after admission he was operated on under spinal anesthesia. There was still some fluid in the peritoneal cavity. Adhesions of the ileum to the cecum were noted, and there was a stenotic lesion at the ileocecal junction with tremendous distention of the ileum, which was larger than twice the size of the colon. The ileum had the characteristic thickening and hose-like rigidity of regional enteritis. A resection of 18 inches (46 cm.) of the terminal ileum, the cecum and the ascending colon to the middle of the transverse colon was done. Postoperatively the patient received one more transfusion. He made an uneventful recovery with primary wound healing. Sixteen days following the day of his operation despite the transfusions the blood protein was 4.4; the albumin was 2, and the globulin was 2.4. Twenty-one days postoperatively the total protein was 5.3; the albumin was 2.3, and the globulin was 2.92. Twenty-seven days postoperatively the total protein was 6.24; the albumin was 2.56, and the globulin was 3.68. There was still an inverted albumin-globulin ratio of 0.7.

The protein concentrations in this case were lower than any in our series of disruptions, low enough to result in nutritional edema, and yet the wound healed without dehiscence.

There is a voluminous literature on the healing of wounds, but information regarding the role of serum protein is meager. There are some facts concerning the effect of diet on wound healing, and from these many inferences have been drawn, some of which at least may be unwarranted. Thus Clark<sup>6</sup> showed that the latent period in wound healing (the time from the injury up to the time of fibroblast proliferation of Carrel<sup>7</sup>) may be shortened almost to the point of elimination by a protein diet. The fact that proteins stimulate cellular proliferation has been shown in other ways.<sup>8</sup> Harvey and Howes,<sup>9</sup> studying wounds in the stomach, found no diminution in the latent period with a high protein diet, but noticed an increased velocity of fibroplasia and its earlier termination once the process was initiated. As a result the maximum strength of the wound was attained earlier than with animals on a standard diet. Howes, Briggs, Shea and Harvey<sup>10</sup> found that the rate of return of tensile strength in adult rats was not affected by complete or partial starvation, although a half adequate diet did result in retardation in young rats. Similarly Morgan<sup>11</sup> showed that regeneration after amputation of legs of salamanders occurred as rapidly during starvation as when they were well fed.

Thompson, Ravdin and Frank<sup>12</sup> reported that the abdominal wounds of 8 of 11 dogs previously fed a restricted diet and subjected to repeated plasmapheresis disrupted or failed to heal. They with Rhoads<sup>13</sup> subsequently failed to obtain disruption in 3 similarly prepared dogs which

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6. Clark, A. H.: The Effect of Diet on the Healing of Wounds, *Bull. Johns Hopkins Hosp.* **30**:117, 1919.

7. Carrel, A.: The Treatment of Wounds, *J. A. M. A.* **55**:2148 (Dec. 17) 1910.

8. Doberauer, G.; Hoke, E., and Pittrof, E.: Experimentelle Untersuchungen über Wundheilung, *Med. Klin.* **12**:853, 1916. Herrmannsdorfer, A.: Ueber den Einfluss der Nahrung auf die Pufferkapazität des Blutes und den Heilverlauf und Keimgehalt granulierender Wunden, *Deutsche Ztschr. f. Chir.* **200**:534, 1927. Reimers, C., and Winkler, H.: Experimentelle Untersuchungen zur Wundheilung und ihre Beeinflussung durch "Azidose" (saure Kost), *ibid.* **241**:313, 1933.

9. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on Velocity of Growth of Fibroblasts in Healing Wounds, *Ann. Surg.* **91**:641, 1930.

10. Howes, E. L.; Briggs, H.; Shea, R., and Harvey, S. C.: Effect of Complete and Partial Starvation on Rate of Fibroplasia in Healing Wound, *Arch. Surg.* **27**:846 (Nov.) 1933.

11. Morgan, T. H.: The Physiology of Regeneration, *J. Exper. Zool.* **3**:457, 1906.

12. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, *Arch. Surg.* **36**:500 (March) 1938.

13. Thompson, W. D.; Ravdin, I. S.; Rhoads, J. E., and Frank, I. L.: Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, *Arch. Surg.* **36**:509 (March) 1938.

postoperatively received lyophilized serum intravenously to raise the serum protein content. They suggested that hypoproteinemia was a factor in the mechanism of disruption and that retardation in healing of wounds associated with hypoproteinemia might be averted by restoration of the serum protein to normal levels immediately after operation.

Unfortunately their papers contain no data on the actual concentration of serum protein and its fractions, the percentage of disruptions in the 8 dogs whose wounds were considered to have unsatisfactory healing or the relation of infection to the unsatisfactory healing in those of the 8 dogs without disruption. Then too, while protein starvation and repeated plasmapheresis do produce hypoproteinemia, there is little evidence that it is the only metabolic disturbance in animals treated in this manner. Thus it is difficult to evaluate their results or to apply them to the problem in human beings.

Since there is no direct evidence of the importance of a high serum protein level for satisfactory wound healing, in the light of our findings it seems fair to say that at present the poor nutritional state of which hypoproteinemia is a manifestation may favor wound disruption.

#### SUMMARY

Data on total protein concentration in 1,358 consecutive admissions to a surgical service are presented. In this series there were 4 cases of wound disruption; in all of these there was a relatively high concentration.

The average serum protein concentration in 40 cases of wound disruption was significantly lower than in 40 cases of control well healed wounds.

The occurrence of relatively high serum protein concentration in cases of wound disruption and low concentration in cases of well healed wounds suggests that hypoproteinemia by itself is neither a necessary nor a sufficient cause for wound disruption.

A poor nutritional state of which hypoproteinemia is a manifestation may favor wound disruption.

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# NEW METHODS FOR DETERMINING THE VIABILITY OF BOWEL

PRELIMINARY REPORT WITH CLINICAL CASES

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The establishment of the viability of the bowel in cases of strangulated hernia is of great importance in abdominal surgical procedures at the time of operation since resection of the bowel considerably increases the operative hazard.

In Frankau's<sup>1</sup> series of cases of strangulated hernia immediate resection and anastomosis showed a mortality rate of 42.8 per cent, while in cases in which resection was not done the mortality rate was only 14.7 per cent. In the series of Braun and Wortmann<sup>2</sup> the mortality rate associated with resection was 50.4 per cent, while in their cases of strangulated hernia in which resection was not done the mortality rate was only 14.8 per cent. Since the decision concerning the viability of the intestine must be made within a short time after the abdomen is opened, the surgeon often finds himself in a quandary as to whether or not the intestine is beyond recovery. Stone<sup>3</sup> stated that this is one of the many occasions when the widest experience may prove fallacious and the best judgment faulty. The extremes, as usual, are

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The fluorescein solution used in this study was supplied by C. F. Kirk & Co., New York.

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1. Frankau, C.: Strangulated Hernia: Review of 1,487 Cases, *Brit. J. Surg.* 19:176-191 (Oct.) 1931.

2. Braun, W., and Wortmann, W.: *Der Darmverschluss und die sonstigen Wegstörungen des Darmes*, Berlin, Julius Springer, 1924.

3. Stone, H. B.: Hernia, in Lewis, D.: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 7, chap. 9, pp. 1-66.

easily dealt with. It is the intermediate case in which decision is difficult. But this decision, if erroneous, may lead to death in a great number of cases.

The methods now used in doubtful cases rely mainly on the return of pulsation in the arteries of the bowel segment concerned and on the return of a pink color, especially after warm compresses have been used for some time. This procedure in turn prolongs the operation and may add further hazards, particularly the damage to the serosa produced by the hot pads used in laparotomy. Thus far no method has been devised which shows immediately and objectively whether the circulation in the bowel will be reestablished after strangulation is released.

The following possibilities have presented themselves, namely, the use of fluorescein, the local use of procaine hydrochloride and the inhalation of pure oxygen. This investigation was given impetus by Dr. Herbert C. Chase, who employed oxygen for the recognition of viability of the intestine in dealing with loops presenting doubtful circulatory competence. A subsequent report will deal with the application of oxygen and also with the effects of the various types of anesthesia in relation to the viability of the bowel.

#### FLUORESCEIN TEST

Recent observations in our laboratories proved that the fluorescent effect of fluorescein,<sup>4</sup> which had been used in the objective determination of circulation time,<sup>5</sup> would also reveal the presence and adequacy of circulation in the intestine. Since then the opportunity for further study of this phenomenon presented itself both in experimental animals and in 6 patients with strangulated hernia.

The fluorescein test is performed as follows: After exposure of the questionable loop of bowel and release of the strangulation, the operating room is slightly darkened, and the color of the intestines is observed under purple light. Fatty parts of the mesentery may show a yellowish tint owing to a certain fluorescence inherent in adipose tissue. Five to 6 cc. of a 5 per cent solution of fluorescein (in dogs 1 cc. only is used) to which sodium bicarbonate is added to make a 5 per cent solution is then rapidly injected intravenously. The rays of an ultra-violet bulb which is covered with a purple glass filter (Wood filter) are directed by an assistant into the questionable loop of bowel. This special filter permits the passage of only a wavelength of 3,500 to 4,000

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4. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, *M. Clin. North America* **26**:943-952 (May) 1942.

5. Lange, K., and Wollheim, E.: The Circulation Time and Its Relation to Other Factors of the Circulation, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **43**: 134-140, 1931.

angstrom units, thus giving a dark purple light effect on the tissue. After the circulation time has elapsed, the fluorescein appears in the vessels of the bowel, producing a characteristic golden green illumination of only those areas sufficiently supplied with blood. Districts which are not viable and accordingly out of circulation remain purple, while other segments inadequately supplied show markedly diminished illumination and often have a patchy character. These effects are so conspicuous that the naked eye easily observes the entrance of blood into the smaller vessels and the further spread into the serosa.

Fluorescein seems to be nontoxic. We have given up to 15 cc. intravenously in clinical cases and have examined nearly 500 patients with the method. We were unable to observe reactions of any kind in this series. Fluorescein is rapidly excreted into the urine, and with a normal renal function it is no longer visible in the plasma after five hours have elapsed.

#### PROCAINE HYDROCHLORIDE

Recent advances in the knowledge of peripheral vascular diseases suggested the application of our newer knowledge of the effects of procaine hydrochloride on circulatory changes in the bowel. The marked objective changes in the intestine could readily be accounted for by the end results of vasospasm which in itself is reflex in character. Furthermore, the established efficacy of procaine hydrochloride in releasing arterial and venous constrictions by means of inhibiting the autonomic impulses could be applied in the investigation of the circulatory competency of the intestine. These principles were applied in our experimental and clinical cases with excellent results.

#### EXPERIMENTAL EVIDENCE

In a series of 7 rabbits a strangulation of the intestine was produced by putting a rubber band under an exact predetermined tension around a loop of small bowel about 3 inches (7.6 cm.) long. The pressure exerted at the place of constriction was always far above the systolic pressure. This strangulation was maintained for different periods as shown in the table.

After the rubber band was released, fluorescein was injected intravenously, and the appearance of the strangulated loop in contrast to the normal bowel was observed. Up to a time limit of two hundred and twenty minutes, full fluorescence of the formerly strangulated loop appeared within a few seconds; only beyond this period parts of the bowel failed to show full fluorescence. Small serosal areas maintained a persistent purple hue. After two hundred and fifty-five minutes, however, no return of fluorescence after injection of the solution could be noted; this was evidence that the vascular tree leading to this area was definitely occluded. Hot pads failed to restore the circulation in this particular loop. One fact, however, was conspicuous. Even in those animals in which the duration of strangulation was only two hundred minutes, the gross appearance of the bowel was altered in color

to so great a degree that surgical judgment would have suggested resection in a comparable clinical case. Immediate recovery of the circulation was revealed by the fluorescein test. It was felt that the intensity of the color changes in the production of strangulation was primarily due to venous congestion.

Using a sharp clamp for occluding the vessels of the intestine, irreversible damage to the vessels, indicated by an entirely negative or patchy reaction to the fluorescein test, was produced in 4 rabbits after twenty-five minutes.

In a series of 5 dogs the strangulation of the small bowel by a rubber band of exactly predetermined tension was repeated. These tests, however, were modified by injecting 2 per cent procaine hydrochloride around the main vessels leading to the strangulated district. This method, which had already proved its diagnostic and therapeutic value to two of us (S. T. G. and J. O. H.), showed its merits also in these objective tests. Two loops of small bowel were strangulated under the same pressure, and after a certain period (when the involved portion of intestine appeared dark or was approaching a black color) both strangulations were released. At the same time fluorescein was injected intravenously, and the intestine was exposed to the special light. It could be noticed that in all cases in which procaine hydrochloride had been injected into the mesentery of one of the loops this loop showed an earlier,

*Duration of Strangulation and Restoration of Circulation in Experimental Animals*

Animals	Duration of Strangulation (Min.)	Restoration of Circulation	
		Complete	Partial
1	60	+	
2	150	+	
1	220	+	
1	220	—	+ (Patchy fluorescence)
2	255	— *	

\* No restitution after 300 min.

more homogeneous and more intense fluorescence than the loop not treated in this manner. If in the loop with the untreated vessels only patchy fluorescence could be seen for some time, injection of procaine hydrochloride along the vessels leading to such a segment often produced an immediate return of circulation and peristalsis in the area which had previously been purple.

A more rapid response to procaine hydrochloride was noted when the injection was made at the mesenteric border of the bowel than when the injection was made around the larger vessels. This observation was even more noticeable at the site of the constriction rings. It has not been determined whether procaine hydrochloride exerts an additional effect on the smooth muscle of the intestine aside from the effect on its autonomic nerve supply.

Since in strangulated hernias the serosa sometimes is found torn or scraped off the muscularis, we reproduced this condition by stripping part of the bowel of its serosa. Under normal conditions such denuded areas are less transparent and contain considerably fewer capillaries. This accounts for the markedly diminished intensity of the fluorescence in the absence of serosal tissue. However, if normal circulation prevails in this region of exposed muscularis, a few capillaries always show up with good fluorescence, and if this is not the case, injection of procaine hydrochloride along the vessels supplying the area makes them appear immediately.

## CLINICAL EVIDENCE

CASE 1.—W. C. had right inguinal hernioplasty performed for an incarcerated inguinal hernia on Sept. 13, 1941. General anesthesia was used. The hernial sac was dissected free of the scrotum. A strangulated loop of small intestine was found when the sac was opened. The portion of intestine was approximately 10 cm. in length and blackish in color for a distance of 6 cm. The patient was given 100 per cent oxygen by inhalation, and warm laparotomy pads were applied on the bowel. After a lapse of five minutes there was practically no return in circulation. Procaine hydrochloride (5 cc. of 2 per cent solution) was injected into the root of the corresponding segment of the mesentery around the blood vessels. Within one minute the bowel had acquired a pinkish hue, and active peristalsis developed throughout the affected part of the intestine. The bowel was then replaced into the peritoneal cavity, and the wound was repaired in the usual manner. Recovery was uneventful.

CASE 2.—J. K. had left inguinal hernioplasty performed for incarcerated inguinal hernia on March 25, 1942. General anesthesia was used. When the hernial sac was opened, a large amount of hemorrhagic fluid escaped. A loop of strangulated small intestine about 10 cm. in length was released; its walls were purplish, congested and edematous. An intravenous injection of fluorescein was given, and the intestine was inspected under the ultraviolet light. An area about 3 by 4 cm. showed no circulation. Hot packs were applied, and 100 per cent oxygen was given by the closed system. Moderate improvement was noted, but there still remained a segment of the intestine about 2 cm. in length which was devoid of circulation as shown by the fluorescein test. About 10 cc. of 2 per cent solution of procaine hydrochloride was injected into the mesentery corresponding to the involved loop, and within two minutes following this procedure fluorescence was noted throughout the involved region. The intestine was returned to the peritoneal cavity. Repair of the wound was done in the usual manner. Recovery was uneventful.

CASE 3.—J. W. had right inguinal hernioplasty performed for incarcerated inguinal hernia and hydrocele. General anesthesia was used. A large amount of hemorrhagic fluid escaped when the hernial sac was opened. Approximately 45 cm. of the small intestine was found to be strangulated. Oxygen (100 per cent) was administered by mask. The color of the intestine which had been deep purplish became lighter. Peristalsis, however, was not visualized. About 10 cc. of 2 per cent solution of procaine hydrochloride was injected into the corresponding root of the mesentery, and within thirty seconds active peristalsis was visible. The intestine was returned to the peritoneal cavity, and the usual repair was performed. Recovery was uneventful.

CASE 4.—J. Z. had left femoral hernioplasty performed on Jan. 14, 1942, for a strangulated femoral hernia. Local anesthesia was used. When the hernial sac was opened, about 4 inches (10.2 cm.) of gangrenous small intestine was found. The mesenteric vessels of this segment were thrombosed. An intravenous injection of 5 cc. of fluorescein was given. Under the ultraviolet light excellent fluorescence limited by the blackened gangrenous area was noted. The line of demarcation between the fluorescence and the involved portion of the intestine was sharp. Hot packs, oxygen (100 per cent) by inhalation and injection of procaine hydrochloride into the mesentery failed to revive the gangrenous portion of the intestine. Side to side anastomosis was performed following the resection of the nonviable bowel. Repair of the wound was performed in the usual manner. Postoperatively, the abdominal status was satisfactory; however, the patient died on the tenth day as a result of pneumonia.



CASE 5.—M. A. had left femoral hernioplasty performed on April 1, 1942, for an incarcerated femoral hernia. General anesthesia was used. When the sac was opened, about 10 cm. of small intestine was found to be incarcerated. The application of hot packs and the inhalation of oxygen (100 per cent) gave only slight improvement. The fluorescein test revealed the absence of circulation. Within two minutes after the injection of 4 cc. of 2 per cent procaine hydrochloride along the corresponding mesentery, peristalsis became visible, and the color of the bowel returned to normal. At this time fluorescence was definite. The wound was repaired in the usual manner. Recovery was uneventful.

CASE 6.—K. W. had right inguinal hernioplasty performed on Nov. 11, 1941, for an incarcerated recurrent inguinal hernia. Local anesthesia was used. The peritoneum was opened in the floor and was found to consist of incarcerated omentum. The patient was given 2.5 cc. of a 5 per cent solution of fluorescein intravenously; the room was darkened, and the portion of the omentum the viability of which was questioned was exposed under the ultraviolet light. The absence of fluorescence in the involved omental mass indicated the lack of circulation, and a portion 8 by 10 cm. was resected. The repair was performed in the usual manner. An uneventful recovery followed.

#### COMMENT

The application of the findings revealed in the animal experiments was exactly borne out in 6 patients, as just reported. After the strangulation was released and the intestine was observed under the purple light, 5 to 6 cc. of 5 per cent solution of fluorescein was given intravenously and the special light directed on the portion of intestine the viability of which was doubtful.

Five hernias contained small bowel, and 1 contained omentum. In all cases the clinical course after operation bore out the correctness of the prognosis based on the fluorescein test, the procaine hydrochloride test or both. In 3 cases only could patchy fluorescence be obtained in parts of the strangulated loop. In 2 of these procaine hydrochloride succeeded in releasing the spasm. In 1 case, however, this attempt failed, and resection was performed. In 2 cases, judging from the gross appearance of the bowel, resection seemed inevitable, but the combined fluorescein-procaine hydrochloride test resulted in satisfactory restoration of the circulation thereby obviating resection. The clinical course in these cases was uneventful, corroborating the prognosis. In 1 case a localized serosal defect failed to show fluorescence. However, injection of procaine hydrochloride along the larger vessels caused the appearance of fluorescence in the muscularis within a few seconds, giving evidence of the return of blood supply to this region.

In many of our animal experiments as well as in 3 of our cases it was evident that the contraction ring at the place of incarceration had not disappeared during the period of observation, although this same district showed homogeneous fluorescence from the beginning. The persistence of the contraction ring, therefore, cannot be considered a proof of nonviability of the bowel.

## SUMMARY

A method in which fluorescein is used is described whereby direct visual evidence concerning the viability of an injured portion of the intestine can be established immediately.

Procaine hydrochloride injected along the vessels leading to a strangulated loop of intestine is able to release vascular and muscular spasms, thereby restoring the viability of the intestine. It serves not only as a diagnostic agent but also as a therapeutic measure.

The time of strangulation is the most essential factor for the return of circulation in the bowel thus damaged.

The persistence of the contraction ring at the point of strangulation cannot be considered a valuable diagnostic sign of nonviability of the bowel.

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## PROGRESS IN ORTHOPEDIC SURGERY FOR 1941

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE  
AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

(Continued from Page 690)

### VII. INFECTIONS OF BONES AND JOINTS, EXCLUSIVE OF TUBERCULOSIS

*General Considerations.*—Owen,<sup>232</sup> discussing acute hematogenous osteomyelitis, reemphasizes that it is a blood-borne pyogenic infection affecting principally the long bones of children and adults. The early diagnosis is made on the basis of sudden onset of fever, pain, localized deep tenderness and limitation of motion. The original infection is from some distant focus. The author stresses the fact that the earliest local signs are heat and increased tenderness on deep pressure with a normal roentgen picture. The infection spreads rapidly along the medullary cavity, starting in the metaphysis distal to the entrance of the nutrient artery. There is a plugging of part or all of the arterial tree with abscess formation, and as the infection spreads along the medullary canal and through the haversian canals it reaches the periosteum, which becomes undermined and stripped up.

The author stresses the fact that the treatment must be an individual one and proportioned to the type and the severity of the condition in each case. He states that routine early radical operation causes a higher mortality rate in cases in which the condition is acute but feels that in cases in which a single bone is involved drainage should be instituted quickly.

In addition to operation, parenteral administration of fluids, transfusions, constant nursing care, sedation if necessary, absolute rest in bed and splinting of the limb in the selected position should be routine.

In the cases in which the condition was acute the mortality rate has been 13 per cent, and in the cases in which the condition was chronic, 1 per cent.

[ED. NOTE: This is a good article on the general consideration of acute hematogenous osteomyelitis. We also feel that conservatism should be the keynote of the care in cases in which the condition is acute.]

In considering subacute osteomyelitis Forni<sup>233</sup> reports in detail a case of subacute cortical diaphyseal osteitis in a boy of 18 years. He

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232. Owen, W. B.: Hematogenous Osteomyelitis, *South. M. J.* **34**:544-547 (May) 1941.

233. Forni, G.: Subacute Cortical Diaphyseal Osteitis in the Adult, *Rassegna internaz. di clin. e terap.* **22**:81-95 (Feb. 15) 1941.

concludes from a review of the literature that the condition is rare in adults and is usually caused by the staphylococcus, being most frequently observed in young men and varying in type according to the degree of virulence of the organism. In the differential diagnosis one has to consider osteogenic tumors in general and Ewing's tumor in particular, the chronic inflammatory disease of bone and melorheostosis. The treatment is chiefly surgical, and autogenous vaccines may be used as an adjunct to operation.

In the case which the author describes, syphilis was suspected, but the tests yielded negative results. An operation was performed, and the patient was discharged one month later. When seen six months later, he seemed well and was about to enter military service. The symptoms, however, recurred as evidenced by swelling in the lower part of the thigh; this was first diagnosed as sarcoma. At the second operation small purulent foci were found in the cortex, surrounded by granulation tissue. The cavity was disinfected with ether and packed with ointment, and the limb was placed in a plaster cast.

Histologic examination showed marked density of bone. Staphylococcus aureus was isolated, and this organism was found responsible in 11 of 20 cases. The course of the disease in the adult is attributed to an attenuated virulence which produces necrosis rather than suppuration. In some cases there has been a gradual involvement and muscular atrophy. The author states that in about 76 per cent of the cases reported in the literature the patients were females between 11 and 31 years of age.

[ED. NOTE: Acute or subacute osteomyelitis in adults is certainly not common.]

In reviewing osteomyelitis Cleveland<sup>234</sup> reports 56 cases of patients treated within the last ten years. He found that in 80 per cent of the cases osteomyelitis was caused by staphylococcus and in the majority of the other cases by streptococcus. Osteomyelitis due to streptococcus tended to give primary joint involvement and was usually found in infants.

In 16 of the total number of cases, involvement of the upper femoral metaphysis invariably caused secondary invasion of the hip joint with subsequent disability. In 4 of the 17 cases in which the lower femoral region was involved, the knee joint was affected.

Plaster of paris immobilization will lessen the chance of pathologic fracture. For the whole series there was a mortality rate of 25 per cent. Of the patients surviving only one third presented disability. In 34 cases of acute hematogenous osteomyelitis of this series there was a

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234. Cleveland, M.: Osteomyelitis and Pyogenic Infections of Joints, Bull. New York Acad. Med. 17:205-220 (March) 1941.

mortality rate of 8.8 per cent. Conservative operation combined with supportive measures was used in all cases.

[ED. NOTE: This is a comparatively low percentage of both mortality and disability, particularly since many of these patients must have been treated without the benefit of chemotherapy.]

Beranger<sup>235</sup> describes a nonsuppurative generalized form of staphylococcic osteoperiostitis in an infant. In the child during infancy there developed recurring attacks of pain and swelling in the right leg, usually without fever, and at 14 months the child was in poor general condition. He presented septicemia, and throughout the course of his illness the roentgenograms revealed no abnormalities except marked sclerosis and periostitis. The patient finally died in spite of toxoid therapy and various types of conservative treatment, the condition being diagnosed hematogenous nonsuppurative diffuse osteomyelitis. The author feels that this was probably a case of Ollier's albuminous osteoperiostitis.

Lewis<sup>236</sup> presents 9 cases for differential diagnosis in which the roentgen appearance was misleading. Two of the patients were thought to have tuberculosis when first seen, and 2 others showed a similar roentgen picture but were considered nontuberculous. One of the patients proved to have a giant cell variant, and of 2 patients with os calcis disease and identical roentgen findings, one was proved to have staphylococcic, and the other a tuberculous, infection. [ED. NOTE: This roentgen study indicates the difficulty and the futility of differential diagnosis of bone lesions based on roentgen examination alone.]

*Causation and Pathologic Characteristics.*—Bertelsmann<sup>237</sup> presents a discussion of osteomyelitis based on a personal bacteriologic study. He believes that infection may occur in infancy and persist throughout life as a latent infection without symptoms, which will under varying conditions produce osteomyelitis. An injury is to be considered only as a releasing factor, producing exacerbation of an already existing disease, but not as the cause of osteomyelitis except under unusual circumstances. The author is of the opinion that the bacteriologic examination of the blood is of great importance for early diagnosis, for early operation and for the differentiation of mild and severe cases. General hygienic measures, including nutrition in the prenatal period, may help to further reduce the incidence of osteomyelitis. He believes

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235. Beranger, R. P.: Prolonged, Nonsuppurative Generalized Form of Staphylococcic Osteoperiostitis in an Infant: Case Report, *Dia méd.* **13**:222-224 (March 31) 1941.

236. Lewis, R. W.: Cases of Nonspecific Bone Infection with Unusual or Obscure Features, *Am. J. Roentgenol.* **46**:659-666 (Nov.) 1941.

237. Bertelsmann, R.: Hematogenous Osteomyelitis, *Monatschr. f. Unfallh.* **47**:237-247 (Aug.) 1940.

that if the infection develops following an injury to the metaphysial region that *Staph. aureus* was probably present at this site before the injury.

Goodyear<sup>238</sup> discusses the causation and the pathogenesis of purulent polyarthrititis due to *Streptococcus viridans*. He presents a case of infection occurring in a 7 week old infant in which the elbow, the shoulder and the mandibular joints were involved and believes that the infection was transmitted from the mother before birth. [ED. NOTE: Proved *Str. viridans* in an infant of 7 weeks is rare, and the author infers that temporary immunity is not always present in early life and that it may be overcome by a massive infection.]

Canavero and Maggi<sup>239</sup> discuss the classic Lexer osteomyelitis experiments demonstrating that a local bone lesion can produce osteomyelitis only if pus-forming organisms are already circulating in the blood. The authors have confirmed the experiments of Lexer. Twenty-five rabbits were given injections of pathogenic anaerobes. Purulent or necrotic processes in the bone marrow or the diaphyses of the long bones were not produced. After repeated injuries to the surface of the bone, however, a similar injection produced the characteristic osteomyelitic foci and a marked local reaction.

Richardson and Ranking<sup>240</sup> report a metastatic bone infection with terminal meningitis caused by *Bacillus coli*. In the case reported the patient was a man of 57 who was vaguely ill and was found to have pus cells and *B. coli* in the urine. Swelling and induration appeared on the right fibula with nodules that were tender and painful, and from these *B. coli* pus was aspirated. The early roentgen examination revealed no abnormalities, but later examination showed extensive involvement of the right tibia and fibula. There was no response to chemotherapy, and the patient died, presenting at autopsy cultures from the sub-arachnoid space which yielded a growth of *B. coli*.

Chandler and Breaks<sup>241</sup> report a case of osteomyelitis of the femoral head and neck caused by *Bacterium necrophorum*. This occurred in a child of 12 years with a draining left ear, pain in the right hip and evidence of generalized sepsis. Pus smears and cultures showed many

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238. Goodyear, E. S.: Purulent Polyarthrititis Due to *Streptococcus Viridans*: Its Occurrence in Infant of Seven Weeks, *Am. J. Dis. Child.* **61**:342-343 (Feb.) 1941.

239. Canavero, M., and Maggi, E.: Experimental Osteomyelitis Due to Pathogenic Anaerobic Bacteria, *Policlinico (sez. chir.)* **48**:1-22 (Jan.) 1941.

240. Richardson, P. L., and Ranking, J. M.: Metastatic Bone Infection with Terminal Meningitis Due to *B. Coli*, *Brit. M. J.* **2**:743 (Nov. 30) 1940.

241. Chandler, F. A., and Breaks, V. M.: Osteomyelitis of the Femoral Neck and Head Caused by *Bacterium Necrophorum*, *J. A. M. A.* **116**:2390-2392 (May 24) 1941.

gram-negative bacilli with bipolar and granular forms. The organisms were anaerobic and identical with *Bact. necrophorum*. The ability of this organism to invade tissue and become localized is demonstrated, and the authors point out that the focus in children is often otitis media with mastoiditis. The authors feel that infection by this organism is more common than is generally supposed. [ED. NOTE: The chronic course of the disease is similar to that of ordinary staphylococcic osteomyelitis.]

Kini and Kesavaswamy<sup>242</sup> discuss the role of smallpox in the production of deformities caused by bone and joint infections, reporting 21 cases of osteomyelitis associated with smallpox and 4 associated with vaccination. In all of the cases in which there were joint manifestations the end result was ankylosis; in 1 of these cases resection of the elbow later gave an excellent result. [ED. NOTE: This interesting report should be recorded, but we have never encountered destructive bone or joint lesions associated with smallpox or directly attributable to vaccination.]

Tunick and Stone<sup>243</sup> report a case of osteomyelitis in which nine bones in the body were involved following prostatic abscess and bilateral bronchopneumonia. In this case in the chronic stage there was no spontaneous sequestration or development of draining sinuses over a three year period, and a gram-negative Friedländer bacillus was found. Some authors consider this bacillus as only a secondary invader, but Tunick and Stone state that the Friedländer bacillus is found in 10 per cent of the cases of croupous pneumonia and in 23 per cent of the cases of bronchopneumonia.

Jensen<sup>244</sup> presents a case of sclerosing osteomyelitis of the lower end of the femur without suppuration in a 20 year old woman. At operation staphylococcus was found, and the author believes this was a case of chronic sclerosing osteomyelitis of Garré but points out the difficulty of sometimes confusing this condition with syphilis or Ewing's tumor.

*Experimental.*—Scheman, Janota and Lewin<sup>245</sup> discuss the experimental production of osteomyelitis and offer a preliminary report on a method of producing lesions simulating human osteomyelitis. In these

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242. Kini, M. G., and Kesavaswamy, P.: Role of Smallpox in Production of Deformities by Causing Infection of Bones and Joints, *Antiseptic* **38**:169-176 (March) 1941.

243. Tunick, I. S., and Stone, J. R.: Friedländer Bacillus Osteomyelitis, *Bull. Hosp. Joint Dis.* **2**:55-62 (April) 1941.

244. Jensen, D. R.: Chronic Sclerosing Osteomyelitis: Garré, *Am. J. Surg.* **54**:377-383 (Nov.) 1941.

245. Scheman, L.; Janota, M., and Lewin, P.: Production of Experimental Osteomyelitis: Preliminary Report, *J. A. M. A.* **117**:1525-1529 (Nov. 1) 1941.

experiments they were able to keep the animals alive for an indefinite period. Rabbits were used, and a preliminary subcutaneous injection was given a week prior to the inoculation of the tibial metaphysis; 0.3 cc. of sodium morrhuate was injected, and one hour following this, 0.2 cc. of a 1:50 dilution of a twenty-four hour broth culture of *Staph. aureus* was injected into the original metaphysial area.

The authors found that osteomyelitis is invariably produced by this method and that 70 per cent of the animals will live. They therefore feel that further experimentation will be aided by this method of producing the bone infection.

[ED. NOTE: This is an interesting variation and may prove to be of definite practical importance in studying osteomyelitis in animals and human beings.]

Blakemore, Elliott and Hart-Mercer<sup>246</sup> have isolated twenty strains of hemolytic streptococcus using lambs as experimental animals. Fifty-nine cases were studied and 53 cultural growths of hemolytic streptococci were isolated from the suppurative arthritis produced. Intravenous injections into the lambs were followed by sustained bacteremia with periodic intermissions until localization took place. If endocarditis was produced later, this apparently served as a source of continued infection in maintaining bacteremia. It was impossible to infect adult sheep or lambs that had recovered from previous attacks.

In all of the animals dying from joint infections there was found to be marked inflammation of one or more joints, tendon sheaths or bursae, and in 6 of 27 animals endocarditis was present, consisting of streptococcic vegetations, hemorrhages, aggregation of cells and necrotic tissue. These apparently resulted from both emboli and surface implantation and could be compared with acute endocarditis in man.

Suzuki<sup>247</sup> believes that he is the first investigator who has been able to make prolonged studies of experimental pyogenic infection of the bones in guinea pigs. In his series the site of predilection for the hematogenous infection of the bones was not always the metaphysis but sometimes was the diaphysis. In localization of the focus of infection various conditions are of significance. The purulent foci exist more frequently in the metaphysial region if the animals are first brought to a stage of bacterial allergy and thereupon receive injections of small doses of bacilli. This is also true if a sublethal dose is injected into normal animals.

The infection can be more frequently located in the wall of the cortex of the bone if a collodion capsule containing agar and bacilli is placed

246. Blakemore, F.; Elliott, S. D., and Hart-Mercer, J.: Studies on Suppurative Polyarthrititis (Joint Ill) in Lambs, *J. Path. & Bact.* **52**:57-83 (Jan.) 1941.

247. Suzuki, M.: Experimental Studies of Purulent Infection of the Femur and Tibia in Guinea Pigs, *Arch. f. klin. Chir.* **201**:192-231, 1941.



in the abdomen. The author states that the abscess which develops in the periosteum or at the surface of the bone heals and gives the appearance of an exostosis. The primary disease focus in the cortex, usually involving the superficial layer, although occasionally involving the deeper cortical region, becomes necrotic, and between the necrotic and the normal bone there develops an area of lacunar resorption. An abscess is then formed in the bone in which are found necrotic bone fragments. If the infected emboli involve the entire layer of bony substance, an involucrum with a medullary abscess soon develops, but from his experimental work the author feels that the disease focus is usually located in the superficial areas of bone and that the abscess will according to the virulence of the bacteria and the penetration of the disease process form a cloaca toward the periosteum or the marrow cavity. This course is usually toward the marrow cavity owing to the active callous production of the periosteum. The sequestrum always acts as a germ carrier or inflammatory irritant in the center of the purulent focus. A diffuse medullary phlegmon develops with resorption and osteoporosis of the bone, and finally the abscess again perforates the periosteum. The process is repeated with continued necrosis of bone and formation of involucrum. If the bacilli are attenuated or dead, healing with the formation of cicatricial tissue occurs, or a so-called Brodie's abscess may be formed.

The fate of an abscess arising from the metaphysial medulla varies according to whether there is any direct connection with the epiphysial line, and an abscess springing from this area shows a pathologic nature similar to one arising in the true metaphysial region.

[ED. NOTE: The author has written a splendid article, and further experimental observations on involvement of the epiphysial line may shed more light on the growth disturbances so frequently noted in these areas following infection.]

*Regional Involvement.*—In discussing chronic osteomyelitis of the pelvis, Thomsen<sup>248</sup> reviews a series of 37 cases of tuberculous osteomyelitis and 23 cases of purulent osteomyelitis from the Danish Sickness Insurance Association. Pelvic tuberculosis constituted 1.7 per cent of all skeletal tuberculosis and was found in a decreasing order of frequency in the ilium, the sacrum and the pubic bone. Purulent nontuberculous osteomyelitis of the pelvic ring accounted for 8.1 per cent of all of the cases and was located primarily in the iliac bone near the sacroiliac joint. The differential diagnosis is made from the clinical, roentgen and histologic observations, and it should be kept in mind that in the purulent process giant cells may develop. The author analyzes the prognosis in

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248. Thomsen, H.: Chronic Osteomyelitis of the Pelvis, *Acta orthop. Scandinav.* 11:307-341, 1940.

tabular form and shows that the prognosis differs for the tuberculous and nontuberculous infections. [ED. NOTE: Tuberculous disease of the pelvis has been found most frequently involving the acetabulum and the sacroiliac joints, but the great majority of osteomyelitis in the body is undoubtedly nontuberculous.]

The Kovens<sup>249</sup> discuss osteomyelitis of the spine treated by fusion with the use of a bone graft and report 5 cases in which the patients were treated by the Albee method. In all of these cases healing was by primary intention, and the authors favor this method over other fusion methods. They stress the fact that the associated abscesses disappeared without surgical drainage and that their resorption was due both to immobilization and to the increase of local vascularity, this causing increased phagocytosis and immune antibodies. [ED. NOTE: Any method producing immobilization of the diseased part will give an opportunity for healing to occur.]

Holmberg,<sup>250</sup> in discussing septic spondylitis, reports 7 cases, stressing the rare incidence of this infection and suggests that its recognition may become more frequent once its diagnosis becomes less confused with that of tuberculous spondylitis. Staphylococcus or mixed infections of Staph. aureus, Staphylococcus albus and Staphylococcus citreus as well as streptococci and other organisms have all been found to be causative agents. In 74 per cent of the cases the patients were male; 47 per cent of the infections were in the lumbar region and 31 per cent in the dorsal region. There is usually a history of trauma, and the author quotes Iselin, who believes that staphylococci may remain dormant in healthy bone but that they will regain their virulence when there is a vitamin C deficiency.

In 58 per cent of the cases reported in the literature the vertebral arches alone were involved; in 34 per cent the vertebral bodies alone were involved, and both regions were affected in 7 per cent. The ages of the patients reported were 11, 13, 14, 28, 33, 35 and 54 years. The author does not feel that there is evidence enough to prove that trauma is an important causative factor, and in 4 of his reported cases spontaneous healing took place without treatment. Roentgenograms are an aid to early diagnosis because they show shadows of abscesses and soft tissue edema; in 1 of his cases this soft tissue swelling was demonstrated only seven days after the patient became ill.

Treatment consists of incision and drainage with immobilization of the affected part, and the author believes that curettage is unnecessary in most cases. Immobilization is important in the treatment of this

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249. Koven, B., and Koven, M. T.: Osteomyelitis of Spine Treated with Fusion by Bone Graft, *Am. J. Surg.* **53**:13-31 (July) 1941.

250. Holmberg, L.: Septic Spondylitis: Report of Seven Cases, *Acta chir. Scandinav.* **84**:479-504, 1941.

condition. In all 7 cases healing occurred, leaving limitation of motion of the affected part.

[ED. NOTE: This interesting report of nontuberculous osteomyelitis of the vertebrae calls attention to the value of a careful examination. Clinically, in these cases there may be simulation of a tuberculous process to some extent, but the roentgenograms show bone proliferation about the area of destruction, and this is characteristic of a mixed or nontuberculous infection. The idea advanced that relighting of a dormant infection may be due to a vitamin C deficiency is interesting.]

Fridmanas,<sup>251</sup> in discussing hematogenous osteomyelitis of the neck of the femur in children, points out the frequent complication of pathologic luxation or subluxation of the coxofemoral joint as well as the difficulty of early diagnosis. All of his patients were admitted to the hospital late and showed extensive destruction at the coxofemoral region. He advocates aspiration of the joint to prevent luxation in the early stages, and if the process has advanced to a sequestration of the femoral head, he feels that the head should be removed surgically and the neck or the greater trochanter placed in the acetabulum and held there by plaster fixation. Osteomyelitis of the neck of the femur should always be kept in mind in any painful disorders of the hip, and the clinical and roentgen examinations should be carefully made to avoid an incorrect diagnosis, which was made in all 4 cases that the author reports. [ED. NOTE: It seems that the correct diagnosis should not have been missed in all 4 cases.]

Dalton<sup>252</sup> compares the osteomyelitis occurring in the mandible with that occurring in the long bones and notes some of the differences. In 1 case complete sequestration of the jaw without regeneration occurred. He reports 3 cases.

Penhale<sup>253</sup> discusses the early diagnosis and treatment of osteomyelitis of the jaws, stating that the infection generally enters the jaw by way of a tooth cavity and that a hematogenous infection is rare. The disease is unusual in children under 10 years of age. The usual course of the disease in the jaw is that the disease slowly spreads from the region of the tooth along the mandibular nerve giving rise to increased pain. He feels that mandibular osteomyelitis rarely develops following extraction of teeth but that if the infection does develop removal of an infected tooth will sometimes eliminate severe osteomyelitis. Early drainage is necessary, preferably intraoral, and the sequestrums must be removed as they occur. When the diagnosis is in

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251. Fridmanas, J.: Hematogenous Osteomyelitis of the Neck of the Femur in Children, *Medicina, Kaunas* **22**:55-78 (Jan.) 1941.

252. Dalton, V. B.: Osteomyelitic Conditions in Mandible, *J. Am. Dent. A.* **28**:951-956 (June) 1941.

253. Penhale, K. W.: Early Diagnosis and Treatment of Osteomyelitis of Mandible, *J. Am. Dent. A.* **28**:288-297 (Feb.) 1941.

doubt, conservative treatment should be followed. [ED. NOTE: Loss of bone substance following the infection gives rise to asymmetry and is a distressing complication; therefore, early conservative operation is to be done as the author indicates.]

Silver<sup>254</sup> states that following suprapubic prostatectomy there occasionally develops low grade osteomyelitis of the pelvic bones involving particularly the anterior pelvic girdle with varying degrees of disability. [ED. NOTE: This is a rare complication of prostatectomy but should be kept in mind following an unexplained fever, local swelling and tenderness.]

Wheeler<sup>255</sup> reports 3 cases of a condition diagnosed as Sudeck's atrophy which was proved to be periostitis of the pubic bone. He believes that this periosteal thickening with mottled rarefaction of the bones is not true osteomyelitis, for he was unable to reproduce periostitis of the pubes experimentally in rabbits. He believes that it is secondary to nerve injury with acute bone atrophy and that it is a self-limiting disease which lasts from three months to two years. [ED. NOTE: This condition so closely resembles Sudeck's atrophy that we prefer to consider it as falling under this category.]

Cohn,<sup>256</sup> discussing recurrent pyogenic osteomyelitis, reports a case in which the disease remained dormant for forty-seven years and became active following trauma to the old lesion in the tibia. Culture in this case revealed an attenuated form of *Staph. albus* which took forty-eight hours to appear in the culture. [ED. NOTE: There seems to be no time limit to the relighting of an old infection.]

Browder and Meyers<sup>257</sup> discuss infection of the epidural space following vertebral osteomyelitis and feel that sometimes when the symptoms of epidural space infection are manifest it is rare to find roentgen evidence of bony changes in the suspected vertebra. They report 14 cases in only 1 of which there was an osseous lesion, yet in 12 of the 14 cases osteomyelitis was demonstrated at operation, at autopsy or at later roentgen examination. *Staphylococcus* is the usual infecting organism, and surgical drainage should be instituted as early as the condition is recognized. [ED. NOTE: These cases illustrate the difficulty of early diagnosis of infectious spondylitis.]

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254. Silver, C. M.: Pelvic Bone Changes Following Suprapubic Prostatectomy. *Bull. Hosp. Joint Dis.* 2:10-20 (Jan.) 1941.

255. Wheeler, W. K.: Periostitis Pubes Following Suprapubic Cystostomy: Three Cases Diagnosed as Sudeck's Atrophy, *J. Urol.* 45:467-475 (March) 1941.

256. Cohn, B. N. E.: Recurring Pyogenic Osteomyelitis: Report of a Case with Forty-Seven Year Quiescent Period Between Attacks, *Am. J. Surg.* 54:741-743 (Dec.) 1941.

257. Browder, J., and Meyers, R.: Pyogenic Infections of Spinal Epidural Space, Consideration of Anatomic and Physiologic Pathology, *Surgery* 10:296-308 (Aug.) 1941.

Boharas and Koskoff<sup>258</sup> report a case of recurring spinal osteomyelitis with an acute epidural abscess. Spinal puncture in this case yielded pus in the epidural sac, and the authors mention that frequently there is a subarachnoid block. No bony change was noted by roentgen examination or at operation in this case, but on the seventh postoperative day a small sequestrum was removed from the wound; to the authors this was indicative of vertebral destruction.

Richardson and Ranking<sup>240</sup> discuss the question of bone infection followed by terminal meningitis and feel that occasionally *B. coli* is the causative agent.

Butler, Blusger and Perry,<sup>259</sup> in discussing staphylococcic osteomyelitis of the spine, divide the condition into three clinical types.

The first type occurs in children or young adults and is characterized by a sudden onset with symptoms of severe bacteremia. Treatment in these cases is directed toward combating the blood stream infection. The mortality rate is extremely high.

The second type is characterized by a sudden onset with general malaise and pain in the back. An abscess rapidly forms with evidence of pressure on the cord. Meningitis may supervene with fatal results. Drainage of an abscess after laminectomy is probably the best treatment in this type of case.

The third type, the authors feel, is rare and is described as follows: The onset is gradual. The patients are almost always adults. The symptoms are referred to the affected vertebra and often diagnosed as tuberculosis of the spine. The authors report that in 2 cases of this type bone grafting has been done with excellent results.

[Ed. NOTE: This seems to be an unnecessary division of non-tuberculous osteomyelitis of the spine.]

*Therapy.*—Dickson, Diveley and Kiene<sup>260</sup> give a preliminary report on the use of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in the treatment of subacute and chronic osteomyelitis. Twenty-two cases are discussed in this report, in all of which treatment was by local debridement, implantation of sulfathiazole and closure of the wound. Sulfathiazole was given by mouth at least three days preoperatively to insure a blood level of 4.7 per cent.

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258. Boharas, S., and Koskoff, Y. D.: Early Diagnosis of Acute Spinal Epidural Abscess: Report of Illustrative Case, *J. A. M. A.* **117**:1085-1088 (Sept. 27) 1941.

259. Butler, E. C. B.; Blusger, I. N., and Perry, K. M. A.: Staphylococcal Osteomyelitis of the Spine, *Lancet* **1**:480-481 (April 12) 1941.

260. Dickson, F. D.; Diveley, R. L., and Kiene, R.: Use of Sulfathiazole in Treatment of Subacute and Chronic Osteomyelitis, *J. Bone & Joint Surg.* **23**:516-520 (July) 1941.

The technic of operation is as follows: After a tourniquet is applied, the sinus tract is injected with methylthionine chloride, and the sinus is dissected out. The necrotic bone is then removed, and careful saucerization of the bone and excision of the scar tissue are done. Sulfathiazole (1 to 2 Gm.) is then dusted into the wound by a nasal insufflator. The deep soft parts and the skin are then closed by interrupted sutures, and a dressing is applied with moderate pressure. After this the limb is immobilized in plaster. Sulfathiazole is administered for fifteen days after operation. In 14 (78 per cent) of the 18 cases, healing was by primary union; in 2 cases (11 per cent) healing did not occur, and in 2 cases (11 per cent) it was too early to evaluate results. The average healing period was twenty-three days. In this preliminary report the authors urge a further trial of their method.

[ED. NOTE: This article has attracted a great deal of comment, and we believe that the method is of great practical value.]

Key<sup>261</sup> discusses the early operative treatment of acute hematogenous osteomyelitis and reasserts his belief in early operation in the majority of cases. He delays operation only long enough to combat dehydration, and in addition to local chemotherapy he uses antitoxin in selected cases.

Key,<sup>262</sup> in considering the clinical use of sulfonamide drugs in orthopedic cases, defines four types of patients. First there are those with clean operative wounds; for these the dry sterile sulfanilamide was used in 150 cases, sulfathiazole in 70 cases and a mixture of these drugs in 23 cases in which there were nonoperative infections. Secondly there are those with traumatic contaminated wounds; for these the author feels that the local use of these drugs will lessen the incidence of severity of infection when the wounds are sutured or left open. Thirdly there are those with acute pyogenic infections; these infections are of two types: those of locally infected wounds and the acute hematogenous pyogenic infections, such as osteomyelitis and arthritis. In the infected wounds partial débridement, cleansing of the wound and implantation of sulfathiazole with immobilization of the patient are carried out; in the cases of frank osteomyelitis the drug is given by mouth as well as locally, and early drainage is used. Fourthly there are those with chronic osteomyelitis; the author reports that in 14 of 17 cases of chronic osteomyelitis healing by primary union was effected by the method described by Dickson, Diveley and Kiene.

Wilson<sup>263</sup> reports 33 cases of acute hematogenous osteomyelitis and stresses the fact that there is present a disease of the whole organism

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261. Key, J. A.: Early Operative Treatment of Acute Hematogenous Osteomyelitis, *Surgery* 9:657-665 (May) 1941.

262. Key, J. A.: Use of Sulfanilamide and Sulfathiazole in Orthopedic Surgery, *J. A. M. A.* 117:409-412 (Aug. 9) 1941.

263. Wilson, J. C.: Delayed Operative Treatment of Acute Hematogenous Osteomyelitis, *Surgery* 9:666-674 (May) 1941.

and not only a pyogenic infection of the bone. He places his patients in four groups.

In the first are those who were operated on the first seven days of their illness. Of these 62.5 per cent had no metastatic lesions, but 1 out of 4 died. In the second are the patients who were operated on between the seventh and the fourteenth day. Of these 61 per cent had no metastatic lesions, and there were no deaths. In the third are those whose abscesses were drained between the second and the third week from the day of illness. Of these 66.6 per cent had no metastatic lesion, and there were no deaths. In the fourth are those patients who had no operation. Of these 25 per cent died.

He feels that from the high mortality rate in those cases in which drainage was instituted early and in those in which no drainage was instituted that adequate drainage should be done only after the effects of the generalized infection have been overcome.

[ED. NOTE: In general it is felt that conservative operation is the keynote in the treatment of acute osteomyelitis and that radical operation is to be used for chronic osteomyelitis; both are to be aided by local and general sulfonamide therapy.]

Bick<sup>264</sup> reports on 20 cases of hematogenous osteomyelitis and concludes that sulfanilamide and sulfapyridine did not materially affect the course of the process and sounds a word of warning against too much confidence being placed in chemotherapy, feeling that it should never take the place of adequate operation.

Baker<sup>265</sup> compares the results obtained from the use of staphylococcus antitoxin with those obtained from the use of the sulfonamide compounds. In hemolytic *Staph. aureus* infection the ratio of mature to immature polymorphonuclear leukocytes found in the circulating blood can be used to estimate the degree of toxemia and to determine the need for antitoxin therapy. After skin tests for sensitivity have been given, staphylococcus toxins can be neutralized by staphylococcus antitoxin, and the author advises an initial dose of 20,000 units for those under 10 years of age. This is then followed in four hours with an intravenous dose of from 40,000 to 60,000 units, which should be repeated every twenty-four hours thereafter until the proper ratio of the white blood cells is obtained.

Sulfathiazole is of benefit in treating staphylococcic infections, but the author believes that sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) are contraindicated in the presence of

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264. Bick, E. M.: Sulfone Chemotherapy in Hematogenous Osteomyelitis, Surg., Gynec. & Obst. **72**:995-1002 (June) 1941.

265. Baker, L. D.: Acute Osteomyelitis with Staphylococcus Septicemia: Clinical Report on Use of Chemotherapy, and Staphylococcus Antitoxin in Its Treatment, South. M. J. **34**:619-627 (June) 1941.

hemolytic *Staph. aureus* infections. Staphylococcus toxins can be neutralized in vivo by staphylococcus antitoxin prepared from the toxin produced by Burky's Ha strain of hemolytic *Staph. aureus*.

Early and adequate drainage of all foci of infection is necessary if the antitoxin therapy is to be effective.

[ED. NOTE: This excellent study that the author has been pursuing over several years is valuable, and we hope similar studies will be reported by other observers.]

Kuhlmann<sup>266</sup> discusses his treatment for acute osteomyelitis in children. He makes an opening into the medullary cavity with a sharp curet and then immobilizes the limb in a fenestrated plaster cast. He has treated 103 children with acute osteomyelitis with a mortality rate of only 3.88 per cent. [ED. NOTE: It is doubtful that there is any routine treatment for use in all cases of osteomyelitis in children, but conservative operation with supportive measures is felt to be the best in general.]

Foley<sup>267</sup> reports 15 cases of acute hematogenous septic arthritis; in 10 of these, treatment was by aspiration and immobilization. In 6 of these cases the condition was due to streptococcus and in 9 to staphylococcus. Aspiration of the joint was done with the patient under anesthesia induced with pentothal sodium, and the author is convinced of the value of this method of treatment. [ED. NOTE: This is a small series of cases, but it demonstrates the feasibility of extreme conservatism.]

Grasso<sup>268</sup> reports 8 cases in which he feels there was spontaneous development of acute hematogenous osteomyelitis. In 5 cases the femur was affected; in 2 the tibia and in 1 the proximal metaphysis of the humerus were affected. The author concludes that immediate operative intervention is dangerous and superfluous, and he advises absolute early immobilization in lightly padded plaster casts. He believes that the abscess should be incised and that any sequestrums that form should be removed several months later.

Wilensky<sup>269</sup> gives a general discussion of osteomyelitis, emphasizing the distinction between the casual general infection and a consequent local bone lesion. He does not feel that there is any scientific evidence

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266. Kuhlmann, K.: Treatment of Acute Osteomyelitis in Children, *Deutsche Ztschr. f. Chir.* **253**:691-703, 1940.

267. Foley, W. B.: Report on Cases of Septic Arthritis, *Proc. Roy. Soc. Med.* **34**:657-658 (Aug.) 1941.

268. Grasso, R.: Spontaneous Evolution of Acute Hematogenous Osteomyelitis: Expectant Therapy with Early Mobilization and Minimal Intervention, *Polí-clínico (sez. prat.)* **48**:601-617 (April 7) 1941.

269. Wilensky, A. O.: Role of Chemotherapy in Treatment of Acute and Chronic Hematogenous Osteomyelitis, *M. Rec.* **154**:344-346 (Nov. 5) 1941.



to show that chemotherapy will aid the local lesion. [ED. NOTE: One of us (P. C. C.) is not at present committed to only immobilization as a routine practice in the treatment of osteomyelitis. He deplures, however, radical operation in the acute phases of the disease.]

Wilensky<sup>270</sup> reports a case of osteomyelitis of the upper part of the right tibia following paronychia of the left great toe with a positive blood culture. Thrombophlebitis of the saphenous vein over the site of the osteomyelitis developed, and this portion of the vein was ligated and removed. The author points out that this is concrete evidence that the metastatic focus may act as the disseminator of a blood stream infection.

Voznescusky<sup>271</sup> discusses methods of treatment of acute hematogenous osteomyelitis in 414 cases in children. All of the patients were treated by early incision and drainage, and the author feels that when there is a massive involvement of the bone subperiosteal resection of the involved portion should be done if at all possible. He feels that the danger of pseudoarthrosis developing is more hypothetic than real. [ED. NOTE: Resection is practical in only a few locations in the body.]

Gutierrez<sup>272</sup> advocates packing the medullary cavity with muscle tissue; in treating chronic osteomyelitis in the humerus he uses the deltoid muscle, and in the femur, the vastus lateralis muscle, feeling that the muscle tissue is well supplied with blood vessels and that for this reason he can avoid necrosis and gangrene. [ED. NOTE: Some regions of the body lend themselves particularly well to this method following saucerization, but for other regions impairment of muscle function would result. We believe that adequate operation and use of the sulfonamide drugs will give the most satisfactory results in cases of chronic osteomyelitis irrespective of wound packing with muscle tissue.]

Tait<sup>273</sup> reports 6 cases of osteomyelitis in the small bones of the hands and the feet and 1 in the jaw. In all cases treatment was by high voltage roentgen therapy. Cure was obtained in all but 1 case. The author recommends that 1,000 to 2,000 r be given in the first week. [ED. NOTE: It seems that the series is rather small to justify completely the author's conclusions, although undoubtedly roentgen therapy is at times most beneficial.]

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270. Wilensky, A. O.: Excision and/or Proximal Ligation of Extraosseous Thrombophlebitis in Treatment of Acute Hematogenous Osteomyelitis with Positive Blood Culture, *Surgery* 10:409-410 (Sept.) 1941.

271. Voznescusky, V. P.: Discussion of Methods of Treatment of Acute Hematogenous Osteomyelitis, *Novy khir. arkhiv* 46:22-32, 1940.

272. Gutierrez, A.: Gutierrez Method of Treating Chronic Osteomyelitis, *Rev. de cir de Buenos Aires* 20:143-162 (April) 1941.

273. Tait, R. M.: Treatment of Osteomyelitis of Small Bones with X-Ray, *Canad. M. A. J.* 45:229-231 (Sept.) 1941.

Penberthy and Weller<sup>274</sup> report 19 cases of acute hematogenous osteomyelitis treated with sulfapyridine or sulfathiazole and early drainage. They believe in relatively early and adequate surgical drainage and in the use of these drugs, which apparently limit the complications of this disease.

The LeCocqs<sup>275</sup> believe that neoarsphenamine is a valuable weapon in combating acute osteomyelitis due to *Staph. aureus*. They report on 30 patients, all of whom showed positive blood cultures. Twenty-one of these received neoarsphenamine, and of these 24 per cent died, and 76 per cent recovered. Of 9 patients who received no neoarsphenamine 89 per cent died, and 11 per cent recovered. [ED. NOTE: This is an interesting observation, but with such a small series further evidence is needed to substantiate this observation, and it is to be hoped that the authors will report on a larger series.]

Hoyt, Davis and Van Buren<sup>276</sup> treated 8 patients with acute hematogenous osteomyelitis with sulfathiazole given orally but with no operation. The dosages of sulfathiazole was 1 to 1½ grains (0.6 to 0.9 Gm.) per pound per day for two to five weeks in conjunction with fluids, transfusions and the usual supportive measures. The authors advise immobilization of the limbs during the painful stage and feel that the end results following this method were most satisfactory. In only 2 cases was any disability presented, and in only 2 cases was there limitation of function. No deaths occurred. [ED. NOTE: These are interesting observations, and while the series is small, the results are unusually good. We are still awaiting a report on a large series of cases of acute osteomyelitis treated without operation.]

Heberling<sup>277</sup> reviews 201 cases of suppurative arthritis in which two hundred and twenty-one joints were treated with the Willems method of open drainage and active motion. There were 13 deaths in the series. The procedure consists of an incision into the joint and the suture of a soft rubber drain to the capsule with immediate active motion. In this series there were 24 patients with complicating osteomyelitis of adjacent bones. The author feels that to be successful the Willems treatment must be instituted early after the onset of the disease and should be started as soon as the patient awakens from the anesthetic.

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274. Penberthy, G. C., and Weller, C. N.: Chemotherapy as Aid in Management of Acute Osteomyelitis, *Ann. Surg.* **114**:129-146 (July) 1941.

275. LeCocq, J. F., and LeCocq, E.: Use of Neoarsphenamine in Treatment of Acute Staphylococcus Aureus Septicemia and Osteomyelitis, *J. Bone & Joint Surg.* **23**:596-597 (July) 1941.

276. Hoyt, W. A.; Davis, A. E., and Van Buren, G.: Acute Hematogenous Staphylococcic Osteomyelitis: Treatment with Sulfathiazole Without Operation, *J. A. M. A.* **117**:2043-2050 (Dec. 13) 1941.

277. Heberling, J. A.: Review of Two Hundred and One Cases of Suppurative Arthritis, *J. Bone & Joint Surg.* **23**:917-921 (Oct.) 1941.

Meticulous attention to the postoperative care of these patients is necessary if good functional results are to be expected. [ED. NOTE: It is our experience that the cooperation of the patient necessary to active movement is often lacking.]

*Syphilis of Bones and Joints.*—Palmer<sup>278</sup> states that congenital osseous syphilis affects infants and that there may develop an inability or disinclination to move one or more extremities, giving rise to pseudoparalysis. Improvements followed treatment with sulfarsphenamine, although there was no improvement demonstrable roentgenologically until the patient had received prolonged arsenic therapy. The clinical entity of Parrot's pseudoparalysis is generally caused by a congenital osseous involvement of the affected part either from the bony lesion itself or from the altered muscles of the extremity.

Buchman and Lieberman<sup>279</sup> discuss the prevalence of syphilis in bones and joints in 119 persons with bone and joint lesions of congenital and acquired syphilis out of a total of 89,000 orthopedic patients seen in the outpatient department over a ten year period. Twenty-five of the total number had congenital syphilis, and 94 had acquired syphilis. The incidence of skeletal syphilis among the patients with syphilis under treatment was 5 per cent. [ED. NOTE: The low percentage of syphilis of the bones and joints seen today is in striking contrast to that of earlier reports.]

McCord<sup>280</sup> presents an analysis of 129 Negro fetuses in all stages of gestation and points out that the characteristic features of advanced congenital syphilis are the typical saw tooth serrations noted at the metaphysal area and that positive reactions to Kahn and Wassermann tests are noted in the mother in 90 per cent of the cases. He feels that it is difficult to diagnose syphilis in a fetus weighing less than 500 Gm. [ED. NOTE: Advanced congenital syphilis is frequently recognized by the roentgen findings at the metaphyses; this is probably the more characteristic and constant feature.]

Ancich de Barrios<sup>281</sup> describes 6 cases of a typical syphilitic infection in infants. They presented no specific stigmas and showed normal serologic and roentgen findings in the first few months of observation.

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278. Palmer, T. M.: Parrot's Pseudoparalysis as Manifestation of Congenital Osseous Syphilis, *Urol. & Cutan. Rev.* **45**:76-78 (Feb.) 1941.

279. Buchman, J., and Lieberman, H. S.: Prevalence of Syphilis of Bones and Joints: Report of Statistical Study at Hospital for Joint Diseases with a Review of Literature, *Arch. Dermat. & Syph.* **44**:1-12 (July) 1941.

280. McCord, J. R.: Osteochondritis in Stillborn, *Am. J. Obst. & Gynec.* **42**:667-676 (Oct.) 1941.

281. Ancich de Barrios, E.: Atypical Syphilitic Osteopathies in Infants, *Rev. chilena de pediat.* **11**:720-731 (Nov.) 1940.

Later, however, syphilis with periostitis and osteomyelitis was confirmed. The author mentions that Epstein has distinguished two forms of osteomyelitis, the central and the peripheral form. The author feels that normal serologic and roentgen findings in the early months of life do not exclude the possibility of syphilis and urges prenatal treatment of the mother. [ED. NOTE: This is a difficult diagnosis to make for infants, and the absence of evidence of bony lesions in roentgenograms may be due to the probability that the soft tissue infection precedes the bone infection.]

*Myositis*.—McNally and Case<sup>282</sup> report a case of echinococcic cyst of the psoas muscle in a man of 47 and give a review of the literature. Their patient complained of pain low in the back and a mass in the left psoas muscle region which increased in size. On pathologic examination this proved to be an echinococcic cyst. This patient spent the first eleven years of his life in Italy, but no definite clue could be found as to the source of the infection.

*Fungus Infection*.—Moseley<sup>283</sup> reports a case of actinomycosis in a boy of 17 who gave a history of frequent chewing of grass and leaves. A progressively increasing swelling in the interscapular region with fluctuation of the mass developed, but the roentgenograms showed no lung involvement. Aspiration of the pus showed actinomycosis, and it was felt that this infection probably had entered the body by way of a tooth canal because the patient had recently had an infected tooth removed. The entire fluctuating mass was removed without opening the abscess, and the patient recovered. The value of adequate diet and general constitutional treatment along with iodides and vaccine therapy is stressed, and the author believes that local application of 20 per cent thymol solution was of value following operation.

Nunes d'Almeida<sup>284</sup> reports a case of symmetric actinomycosis of the feet in a man of 49. For the past twelve years this patient had suffered from rheumatism, and roentgenograms revealed destruction of some of the bones of the feet and decalcification of others. Tuberculosis and actinomycosis were both suspected, but the latter was proved histologically, and the patient was given large doses of potassium iodide and radiotherapy. Slow healing and cicatrization resulted. [ED. NOTE: The chronicity of the lesion is striking. Actinomycosis involving the feet is particularly rare.]

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282. McNally, A., and Case, J. B.: Echinococcus Cyst of Muscle: Report of a Case Occurring in Left Psoas Muscle, *Am. J. Surg.* **51**:419-422 (Feb.) 1941.

283. Moseley, H. F.: Unusual Case of Actinomycosis, *J. Bone & Joint Surg.* **23**:359-366 (April) 1941.

284. Nunes d'Almeida, A.: Symmetrical Localization of Actinomycosis in Bones of the Feet, *Lisboa med.* **17**:739-751 (Dec.) 1940.

## VIII. CHRONIC ARTHRITIS

*General Considerations.*—Numerous articles have been written during the past year stressing the general constitutional nature of rheumatoid arthritis and the need for treating it as such.<sup>285</sup> The laboratory findings of Block, Buchanan, and Freyberg,<sup>286</sup> which suggest that jaundice may help because of the concomitant extremely high levels of lipids, phospholipids and cholesterol, are of special interest. The ruling out of arterial disease is of value,<sup>287</sup> but the greatest interest attaches to the general emphasis on the need for treating the individual patient and all his abnormalities of metabolism and function, including his nervous and emotional idiosyncrasies. As Pemberton and Scull<sup>288</sup> say, recovery may be definitely hastened if every disability is considered and every pathologic aspect noted. The problem should include every deviation from normal which is to be found.

Certainly to deny to the struggling arthritic correction of these several deviations because the whole story is not understood and because no one of the factors involved alone induces or "cures" the disease, is to fail to see the problem in the light of all that modern medicine affords.

*Infection as a Causative Factor.*—There is nothing new to report on the subject of infection as a causative factor of chronic arthritis. The two

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285. Kelchner, C. H.: Clinical Aspects of the Etiology of Chronic Arthritis, *Pennsylvania M. J.* **44**:1294-1296 (July) 1941. Andrews, K. R., and Muether, R. O.: Effect of Diet on Arterial and Venous Glucose Tolerance Curves in Rheumatoid Arthritis, *J. Lab. & Clin. Med.* **26**:675-681 (Jan.) 1941. Brown, E. E., and Wasson, V. P.: Capillary Resistance in Rheumatic Children, *J. Pediat.* **18**:328-336 (March) 1941. Spackman, E. W.; Bach, T. F.; Scull, C. W., and Pemberton, R.: Complete Roentgen Ray Studies of Gastrointestinal Tract in Four Hundred Arthritics, *Am. J. M. Sc.* **202**:68-77 (July) 1941. Westcott, W. I.: Experimental Etiology of Arthritis, *Pennsylvania M. J.* **44**:1292-1294 (July) 1941. Zeiter, W. J.: The Prognosis of Rheumatoid Arthritis, *Cleveland Clin. Quart.* **8**:190-197 (July) 1941. Lewis, T. K.: Résumé of Present-Day Treatment of Arthritis, *J. M. Soc. New Jersey* **38**:391-395 (Aug.) 1941. Traut, E. F.: What Every Occupational Therapist Should Know About Arthritis, *Occup. Therapy* **20**:87-91 (April) 1941. Matthews, M. W.: Treatment of Chronic Infectious Arthritis, *New Orleans M. & S. J.* **93**:396-402 (Feb.) 1941. Scull, C. W.: Metabolic Aspects of Arthritis, *Pennsylvania M. J.* **44**:1286-1291 (July) 1941.

286. Block, W. D.; Buchanan, O. H., and Freyberg, R. H.: Serum Lipids in Patients with Rheumatoid Arthritis and in Patients with Obstructive Jaundice, *Arch. Int. Med.* **68**:18-24 (July) 1941.

287. Steinbrocker, O., and Samuels, S. S.: The Arterial Circulation of the Lower Extremities in Chronic Arthritis, *J. Lab. & Clin. Med.* **26**:974-980 (March) 1941.

288. Pemberton, R., and Scull, C. W.: Nutritional Aspects of the Treatment of Arthritis, *Am. J. M. Sc.* **201**:250-262 (Feb.) 1941.

schools of thought continue to argue for or against infection.<sup>280</sup> Vaccines are less considered now than before. Green and Freyberg<sup>290</sup> make the following statement about much discussed brucellosis and arthritis:

Arthralgia and other rheumatic symptoms are common in brucellosis and temporary, non-purulent joint inflammation may occur. Our data indicate that brucellosis is seldom, if ever, a cause of chronic non-purulent joint inflammation.

*Fibrositis.*—Fibrositis as a diagnosis is much questioned in this country. There is an excellent synopsis on fibrositis in the *Annals of the Rheumatic Diseases*, the official journal of the Empire Rheumatism Council of England, for December 1940, which throws more light on the English conception of the disease. Stockman<sup>291</sup> says:

The essential pathology of fibrositis is now well recognized and agreed upon. Under irritation from one source or another the white fibrous tissue of the muscles, nerves, fasciae and other fibrous structures undergoes inflammatory hyperplasia in small patches, the affected areas become swollen and oedematous with serofibrinous exudation, the fibroblasts proliferate rapidly, numerous minute new blood vessels appear, and the whole forms a soft, ill-defined, congested little swelling.

Stockman was the originator of the view that ossifying spondylitis originates as periarticular fibrositis.<sup>292</sup> Buckley<sup>293</sup> feels that the reaction of cells of fibrous tissue may result from trauma, chill, allergy or toxemia. The importance of nodules in diagnosis and treatment he feels is exaggerated. Nodules are common enough but are more often symptomless than otherwise. Harman<sup>294</sup> concludes that the diagnosis of fibrositis rests on the natural history of the disease and its response to injections of procaine hydrochloride into the site of the lesion. Gordon<sup>295</sup> feels that

289. Pilot, I.: Modified Concepts of Focal Infection, *Dis. Eye, Ear, Nose & Throat* **1**:117-120 (April) 1941. Hendricks, E. M.: The Colon as Focus of Infection in Arthritis, *South. M. J.* **34**:652-655 (June) 1941. Bach, T. F.: Focal Infection in Rheumatoid Disease, *Pennsylvania M. J.* **44**:1297-1301 (July) 1941. Gray, J. W.: The Management of Infected Tonsils, Teeth and Sinuses in Arthritis, *J. M. Soc. New Jersey* **38**:178-181 (April) 1941. Wetherby, M.: Intravenous Streptococcic Vaccine Treatment of Chronic Rheumatoid Disease, *Ann. Int. Med.* **14**:1849-1857 (April) 1941. Bohan, P. T.: Chronic Arthritis with Special Reference to Etiology and Management, *Rocky Mountain M. J.* **38**:698-705 (Sept.) 1941.

290. Green, M. E., and Freyberg, R. H.: The Incidence of Brucellosis in Patients with Rheumatic Disease, *Am. J. M. Sc.* **201**:495-504 (April) 1941.

291. Stockman, R.: The Treatment of Sciatica, Brachialgia, and Occipital Headache, *Ann. Rheumat. Dis.* **2**:77-82 (Dec.) 1940.

292. Stockman, R.: Ossifying Spondylitis, *Edinburgh M. J.* **33**:597-605 (Oct.) 1926.

293. Buckley, C. W.: Fibrositis: Some Old and New Points of View, *Ann. Rheumat. Dis.* **2**:83-88 (Dec.) 1940.

294. Harman, J. B.: Fibrositis and Pain, *Ann. Rheumat. Dis.* **2**:101-107 (Dec.) 1940.

295. Gordon, R. G.: The Nature of Fibrositis and the Influence of Psychological States upon It, *Ann. Rheumat. Dis.* **2**:89-99 (Dec.) 1940.

fibrositis represents four different pathologic processes: (1) sudden strain, leading to hemorrhage and the formation of a blood clot which may not be completely absorbed but may become a nodule, which in turn irritates and leads to further attacks; (2) general wear and tear coupled with poor circulation, which leads to the deposition of metabolic waste products and the formation of nodules; (3) chill, leading to local vascular disturbances analogous to those of chilblain with or without nodule formation; (4) psychogenic disturbances, such as worry, which may be responsible for a fibrositic type of pain which is used as a symbol of emotional discontent or may be more marked because the sensorium is oversensitized as the result of some acute emotional disturbance. Chronic emotional disturbances produce endocrine and autonomic disturbances through vegetative controlling centers in the hypothalamic region; these may be followed by fibrositis. Collins<sup>296</sup> states:

The term fibrositis covers in common usage the aetiologically undefined conditions named myositis, myalgia, non-articular rheumatism, panniculitis, and peri-arthritis. . . . A high proportion of cases of fibrositis have an obviously noninfective aetiology. . . . Evidence of inflammation caused by infection in the fibrositic nodule is very slender. Leucocytic infiltration is generally absent. Cultures are always sterile. Reactions of connective tissues to various noxious agents are limited in type. No decision regarding the aetiology of the fibrositic nodule can be made on the available pathological data.

Slot<sup>297</sup> emphasizes the frequency of this type of rheumatic disease among industrial workers and the importance of strains of muscles and ligaments of the neck, the arms, the hands, the back, the gluteal region and the feet as predisposing causes. Race<sup>298</sup> reports that the most useful test is that of the sedimentation rate; this was found to be low in 80 per cent of the cases. Laboratory findings suggest that fibrositis may have a gouty basis.

*Gout.*—Hench<sup>299</sup> has written an excellent paper giving the picture of gout most clearly, with a carefully planned diet free of purines and low in fats. There is nothing new, but the description of the disease is most encouraging. Solomon and Stecher<sup>300</sup> agree with other writers that gout is not a rare disease. They report 79 cases in five years in the

296. Collins, D. H.: Fibrositis and Infection, *Ann. Rheumat. Dis.* **2**:114-126 (Dec.) 1940.

297. Slot, G.: Fibrositis Among Industrial Workers, *Ann. Rheumat. Dis.* **2**:134-140 (Dec.) 1940.

298. Race, J.: Laboratory Findings in Fibrositis, *Ann. Rheumat. Dis.* **2**:127-133 (Dec.) 1940.

299. Hench, P. S.: Diagnosis and Treatment of Gout and Gouty Arthritis, *J. A. M. A.* **116**:453-459 (Feb. 8) 1941.

300. Solomon, W. M., and Stecher, R. M.: Gout: A Prevalent Arthritic Disease, *Arch. Phys. Therapy* **22**:462-466 (Aug.) 1941.

City Hospital, Cleveland. All agree that colchicine should be used. Haden<sup>301</sup> feels that gout is never cured but only alleviated. Oppenheimer,<sup>302</sup> working on hens, reports the fact

. . . that a solution containing uricase, if injected either intravenously or intramuscularly in hens with a "gouty" or high plasma uric acid concentration, will produce a sharp lowering of the uric acid level. The higher the plasma uric acid level, the greater the uricolytic activity of the enzyme. . . . Although the weekly uricase injections do seem to keep the plasma uric acid level lower in hens on a high protein diet, this work has not been in progress long enough to determine whether the relatively small dosage employed will prevent the appearance of tophi. Even the control hens have not had sufficient time to develop gouty tophi.

*Degenerative Joint Disease (Osteoarthritis).*—Stecher<sup>303</sup> in a study of Heberden's nodes decides that there are two types, one resulting from trauma, the other idiopathic. They are profoundly influenced by race, sex and age. Sixty-eight families with Heberden's nodes showed that mothers are affected twice as frequently and sisters three times as frequently as the population in general. There is a hereditary tendency. The author feels that these conclusions apply only to Heberden's nodes. Short and Bauer<sup>304</sup> prefer "degenerative joint disease" as a term rather than "osteoarthritis" since pathologic study clearly indicates that the condition is a degenerative process. In their article they give a complete plan of treatment, and they show that there are

. . . few indications for surgery in the treatment of degenerative joint disease. . . . One is the removal of loose bodies or so-called "mice" from the knee joint if pain, locking or secondary inflammation is caused thereby. Conservative treatment should be given a trial, but if incapacitating symptoms persist and the loose bodies are demonstrable by examination or roentgenograms, removal should be carried out without delay, since the degenerative process may be hastened by their presence. Acute traumatic effusions usually subside with rest and splinting; if they persist, aspiration should be done. Measures to prevent the development of degenerative joint disease or the acceleration of its course, once present, should be obvious to the reader on consulting the list of contributing factors already given. Such measures fall properly into the field of preventive medicine, and constitute one of the responsibilities of both family physician and specialist. In handling fractures and sprains, diseases of the epiphysis, rickets, infantile paralysis and so forth, the physician must bear in mind the possibility of premature development of degenerative joint disease if the joints are left subject

301. Haden, R. L.: Gout, Proc. Interst. Postgrad. M. A. North America (1940), 1941, pp. 259-263.

302. Oppenheimer, E. H.: The Lowering of Blood Uric Acid by Uricase Injections, Bull. Johns Hopkins Hosp. 68:190-195 (Feb.) 1941.

303. Stecher, R. M.: Heberden's Nodes: Heredity in Hypertrophic Arthritis of Finger Joints, Am. J. M. Sc. 201:801-809 (June) 1941.

304. Bauer, W., and Short, C. L.: The Treatment of Degenerative Joint Disease, New England J. Med. 225:145-150 (July 24) 1941.



to unusual strain. Static deformities and postural defects should be corrected as speedily and as completely as possible. Obesity, especially in those approaching middle age, is hazardous to the well-being of the joints, as well as of the other bodily spasm. Repeated joint trauma, whether occupational or recreational, should be advised against. Finally, in a patient with any form of arthritis, the possibility of secondary degenerative changes must always be kept in mind and guarded against, especially if the movements of weight-bearing joints tend to become limited in a position of mechanical strain.

This paper should be read, since the material is far too complete to abstract. Both Bayles and Russell <sup>305</sup> and Bauer <sup>306</sup> agree that degenerative joint disease of the temporomandibular joint is due to trauma of the cartilage. Prognosis is good for functional results. This subject has not been much written about before, so that these articles are interesting. Copeman <sup>307</sup> reports the effect of the use of pneumatic drills in industry: First there is spasm; then small areas of decalcification of bone develop together with disturbances in the blood vessels, conditions affecting the muscles and injuries to the joints. Injury seems to depend on the way the particular joint reacts to vibration. The condition is osteoarthritis dissecans.

*Gold Therapy.*—The evidence increases each year that gold is the best medical agent in the treatment of chronic rheumatoid arthritis. Hartung and Cotter <sup>308</sup> say

. . . gold therapy gives a higher percentage of improvement than any form of therapy yet used by us in the treatment of rheumatoid arthritis.

Gardner <sup>309</sup> reports that 70 to 80 per cent of 250 patients with rheumatoid arthritis treated with aurothiodextrose suspended in oil (solganal B oleosum) in two or more courses showed improvement. In 50 per cent of the recent cases and in 30 per cent of cases of over two years' duration cure was effected. Eight and four tenths per cent of the patients had reactions. Smyth and Freyberg <sup>310</sup> feel that gold therapy is valuable

305. Bayles, T. B., and Russell, L. A.: Temporomandibular Joint in Rheumatoid Arthritis, *J. A. M. A.* **116**:2842-2845 (June 28) 1941.

306. Bauer, W. H.: Osteoarthritis Deformans of Temporomandibular Joint, *Am. J. Path.* **17**:129-140 (Jan.) 1941.

307. Copeman, W. S. C.: The Arthritic Sequelae of Pneumatic Drilling, *Ann. Rheumat. Dis.* **2**:141-146 (Dec.) 1940.

308. Hartung, E. F., and Cotter, J.: The Effect of Gold Sodium Thiomalate Administration on the Bacteriostatic Properties of the Serum in Patients with Rheumatoid Arthritis, *J. Lab. & Clin. Med.* **26**:1274-1284 (May) 1941.

309. Gardner, E. R.: The Use of Gold in Rheumatoid Arthritis, *M. Rec.* **153**:321-323 (May 7) 1941.

310. Smyth, C. J., and Freyberg, R. H.: Experiences with Gold Salts in the Treatment of Rheumatoid Arthritis, *Univ. Hosp. Bull., Ann Arbor* **7**:45-47 (June) 1941.

though not always beneficial. Toxicity is a bar at present. McCarty<sup>311</sup> stresses early treatment. Cecil<sup>312</sup> concludes that in the treatment of rheumatoid arthritis gold therapy offers more than any other known remedy.

In the study of gold therapy Sabin and Warren<sup>313</sup> state that experimentally certain inorganic and organic gold compounds of both the aliphatic and the aromatic series have been found to exert a curative effect on arthritis produced by pleuropneumonic micro-organisms in mice. The greater the dose, the more rapid is the disappearance of the arthritis. Arthritis disappeared in 96 per cent of 171 mice treated, but only in 5 per cent of 77 mice treated with other compounds and in 7 per cent of 70 mice untreated. The earlier the treatment, the more rapid is the cure. Rothbard, Angevine and Cecil<sup>314</sup> draw the following conclusions:

1. Gold sodium thiomalate is an effective chemotherapeutic agent in the prevention of arthritis produced by a hemolytic streptococcus in rats. Its effectiveness is less against a more virulent strain of the same culture.

2. Sulfanilamide and sulfathiazole [2-(paraaminobenzenesulfonamido)-thiazole] are more effective in the prevention of this disease than gold.

3. Neither gold nor the sulfonamide compounds cure arthritis once it is established.

4. *In vitro*, myocrysin [gold sodium thiomalate] is bactericidal under anaerobic conditions.

5. A severe renal injury resulting in death has been observed in rats weighing 100 grams after an injection of 20 mgm. or more of gold.

6. Myocrysin protects rats against hemolytic streptococcus arthritis but since the effective dose is so close to the lethal dose, great caution is necessary in its administration.

Hartung, Cotter and Gannon<sup>315</sup> have studied the excretion of gold and report as follows:

1. Following the subcutaneous administration of gold sodium thiomalate in patients with rheumatoid arthritis, metallic gold can be consistently recovered from the urine, and the twenty-four hour excretion determined.

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311. McCarty, A. C.: The Use of Gold in the Treatment of Arthritis, Kentucky M. J. **39**:107-110 (March) 1941.

312. Cecil, R. L.: Gold Therapy in Rheumatoid Arthritis, Proc. Interst. Postgrad. M. A. North America (1940), 1941, pp. 253-258.

313. Sabin, A. B., and Warren, J.: The Curative Effect of Certain Gold Compounds on Experimental, Proliferative, Chronic Arthritis in Mice, J. Bact. **40**: 823-856 (Dec.) 1940.

314. Rothbard, S.; Angevine, D. M., and Cecil, R. L.: The Influence of Gold Sodium Thiomalate on the Prevention of Hemolytic Streptococcus Arthritis in Rats, J. Pharmacol. & Exper. Therap. **72**:164-174 (June) 1941.

315. Hartung, E. F.; Cotter, J., and Gannon, C.: The Excretion of Gold Following the Administration of Gold Sodium Thiomalate in Rheumatoid Arthritis, J. Lab. & Clin. Med. **26**:1750-1755 (Aug.) 1941.

2. In two instances the urinary excretion of gold approximate 9 and 17.2 per cent of the intake of gold during the period of observation.

3. Gold was found in the urine from 60 to 300 days after administration of gold sodium thiomalate had been stopped.

4. Gold content of the stool in three instances ranged from 0.22 to 0.65 mg. in twenty-four hours.

5. No gold could be recovered from the saliva in the two instances studied.

6. As far as our observations were extended, the administration of sodium bicarbonate by mouth had no quantitative effect on the excretion of gold in the urine.

This confirms the work of Freyberg and co-workers.<sup>316</sup>

*Vitamin D Therapy.*—There has been much discussion about the use of highly concentrated vitamin D. Snyder and Squires<sup>317</sup> report on the use of ergosterol activated by the Whittier method (electrical activation of heat-vaporized ergosterol) in 23 cases: 1. Toxicity was only temporary. 2. There was no consistent change in blood calcium. The sedimentation rate indicated little. 3. Weight increased in most cases. 4. Roentgen studies were of no definite value in determining the clinical progress of the disease. 5. The cases had been observed too short a time and were too few to permit drawing definite conclusions. 6. Beneficial influence of psychic effects was ruled out. The authors conclude that the results indicate that this preparation has definite value and that its use is no more dangerous than other accepted forms of therapy; they point out, however, that it is too early to appraise its value. Farley, Spierling and Kraines<sup>318</sup> conclude that when this type of activated ergosterol is administered in adequate doses and for a long time the beneficial effect is sustained and may be permanent. [ED. NOTE: There have been published claims that this product is less toxic in equivalent doses than are other preparations of activated ergosterol. These claims have, however, been questioned.<sup>318a</sup>] Steinberg<sup>319</sup> has found that vitamin E has a favorable effect on primary fibrositis. He suggests that

316. Freyberg, R. H.; Block, W. D., and Levey, S.: Metabolism, Toxicity, and Manner of Action of Gold Compounds Used in the Treatment of Arthritis; Human Plasma and Synovial Fluid Concentration and Urinary Excretion of Gold During and Following Treatment with Gold Sodium Thiomalate, Gold Sodium Thiosulfate and Colloidal Gold Sulfide, *J. Clin. Investigation* **20**:401-412 (July) 1941.

317. Snyder, R. G., and Squires, W. H.: Follow-Up Study of Arthritic Patients Treated with Activated Vaporized Sterol, *New York State J. Med.* **41**:2332-2335 (Dec. 1) 1941.

318. Farley, R. T.; Spierling, H. F., and Kraines, S. H.: Five Year Study of Arthritic Patients: Laboratory and Clinical Observations, *Indust. Med.* **10**:341-352 (Aug.) 1941.

318a. Freyberg, R. H.: Treatment of Arthritis with Vitamin and Endocrine Preparations, *J. A. M. A.* **119**:1165 (Aug. 8) 1942. Freeman, S.: Irradiated Ergosterol Poisoning, Correspondence, *ibid.* **119**:968 (July 18) 1942.

319. Steinberg, C. L.: Vitamin E in Fibrositis, *Am. J. M. Sc.* **201**:347-349 (March) 1941.

primary fibrositis is a metabolic rather than an infectious process. [ED. NOTE: The personal experience of one of us (G. B.) tends to substantiate this report and indicates that the use of natural-occurring alpha tocopherol is attended with the best results.]

*Roentgen Therapy.*—Popp and Addington<sup>320</sup> report the studies of 24 cases of psoriasis of the nails. In 6 cases the finger nails only were affected; in 18 cases the hands and the feet both were affected. The average duration of the disease was seven years; the shortest was three months and the longest twenty years. The authors' method of roentgen therapy is described. The results are gratifying; there were complete remission in 6 cases and marked improvement in 10, and there was no improvement in only 2. The benefits were lasting for six months to fifteen years. Roentgen therapy is not recommended as a cure, for benefit is at best only temporary; however, it at least helps to overcome disfigurement. Better results were gained in treating the whole hand or foot than just the nails. Smyth, Freyberg and Peck<sup>321</sup> report as follows: In the treatment of rheumatoid arthritis roentgen therapy gave unpredictable and unreliable results, so that treatment except for psychic effect has been abandoned. Significant results were obtained in 74 per cent of 15 patients with spondylitis rhizomelica, which they are studying further. Experience with degenerative disease of joints and nonarticular forms of rheumatism is insufficient to report on as yet. The reason for using roentgen therapy is still a mystery.

*Gonorrheal Arthritis.*—Davis<sup>322</sup> reports 100 per cent recovery from gonorrheal arthritis without recurrence or joint damage of 15 patients treated by daily intradermal injection of 2 cc. 5 per cent solution of azosulfamide.<sup>323</sup> The safety, the simplicity and the effectiveness of this method cause the author to feel that it will supersede other methods of treatment shortly.

*Physical Therapy.*—Ober<sup>324</sup> discusses the treatment needed in the different stages of rheumatoid arthritis as follows: In the invasion stage the symptoms are soreness and stiffness in the morning, and the treatment is the avoidance of fatigue. In the acute stage the symptoms are swelling of the joints, spasm and deformity, and the treatment consists

320. Popp, W. C., and Addington, E. A.: Roentgen Therapy of Psoriatic Arthritis, *Radiology* **36**:98-99 (Jan.) 1941.

321. Smyth, C. J.; Freyberg, R. H., and Peck, W. S.: Roentgen Therapy for Rheumatic Disease, *J. A. M. A.* **116**:1995-2001 (May 3) 1941.

322. Davis, T. H.: Treatment of Gonorrheal Arthritis with Special Reference to Intradermal Therapy with Neoprontosil, *J. Florida M. A.* **27**:396-399 (Feb.) 1941.

323. Azosulfamide is disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate. This substance has been known as prontosil soluble, as prontosil and as neoprontosil.

324. Ober, F. R.: Physical Therapy in Arthritis, *M. Rec.* **154**:144-146 (Aug. 20) 1941.

of rest in bed, the application of heat and splints and mild exercise. For the subacute stage the treatment consists of rest and more freedom; in the chronic stage this treatment is to be continued. When the condition reaches the stage of ankylosis, operation is to be performed. Reiley and Knapp<sup>325</sup> corroborate Kling's reports of 1933 and 1935. They report the cases of 40 patients treated with histamine iontophoresis. Great symptomatic relief, especially of acute myalgia, strain and sprain, was obtained.

*Surgical Procedures.*—Dickson<sup>326</sup> gives two reasons for operation in cases of arthritis: (1) incapacitating disability and (2) necessity of removing a focus of infection which is active. For the disabled operation often means social betterment which makes life more livable. For appraisal two factors are important, namely, the nature of the joint involvement and the extent of the joint damage present. On patients with atrophic arthritis operation should not be undertaken until the joint is reasonably quiescent. On patients with hypertrophic arthritis, operation may be undertaken at this time. The extent of damage determines the type of operation. The three objectives of operation are: relief of pain, correction of deformity and restoration of function. Commonest operations are manipulation, capsuloplasty, synovectomy, arthroplasty and arthrodesis. Synovectomy is an exception; it can be performed when there is still moderate activity. Preston and Hartung,<sup>327</sup> in discussing surgical procedures for arthritic deformities of the knee, give methods of treatment for four types of patients: (1) those with slight flexion contracture, lateral instability and pain on weight bearing, who require osteotomy to correct the deviation in the weight-bearing line; (2) those with moderately severe flexion contractures, who require manipulations, traction and braces; (3) those with severe contracture, who require posterior capsulotomy, and (4) those with the articular surface destroyed, who require arthrodesis of one knee to relieve the weight on the other. The conclusion is that the end results will be good if the method of treatment selected is suitable for the condition present. Closed methods can be used only in the most mild flexion contractures. The authors emphasize simultaneous use of medical and surgical procedures. Swaim<sup>328</sup> continues to emphasize the importance of early adequate rest and splinting for acutely affected joints. They should be

325. Reiley, R. E., and Knapp, M. E.: Symptomatic Relief in Chronic and Acute Arthritides by Histamine Iontophoresis, *Arch. Phys. Therapy* **22**:288-294 (May) 1941.

326. Dickson, F. D.: The Surgical Treatment of Arthritis, *Ann. Surg.* **113**: 869-876 (May) 1941.

327. Preston, R. L., and Hartung, E. F.: The Surgical Treatment of Arthritic Deformities of the Knee, *S. Clin. North America* **21**:593-603 (April) 1941.

328. Swaim, L. T.: Prevention of Deformities in Rheumatoid Arthritis, *Proc. Interst. Postgrad. M. A. North America* (1940), 1941, pp. 25-29.

supported until the active stage is over, keeping motion by careful exercise. Payr<sup>329</sup> states that marked improvement in most deformed arthritic hands can be expected by prevention of deformity by early splinting with casts and leather apparatus. He describes use of injections followed by correction and casts. Splints are well applied and are described. [ED. NOTE: This article should be read by all those interested.] Magnuson<sup>330</sup> reports a high percentage of free-moving painless joints after thorough removal of degenerated cartilage in cases of degenerative joint disease. The denuded areas are covered by fibrocartilage which serves as a substitute. Removal of the synovia was not found necessary. [ED. NOTE: The procedure described presents a new field for attack on this type of arthritis.] Royle,<sup>331</sup> in treating sacroiliac arthritis with sciatica, reports the cases of 4 who after all other methods of fixation had failed had complete relief with no recurrences after operative fixation. He uses one or two screws as he previously described.<sup>332</sup>

*Arthritis in the Armed Forces.*—Mester,<sup>333</sup> a surgeon in the Polish army, points out that the problem of rheumatism in the army is different from that in civilian life, for the patients all do work of the same type; they fall in definite age groups; they are usually of a good healthy type, and there is the possibility always of conscious and unconscious simulation of the disease. Acute rheumatic fever is not difficult to diagnose, but early rheumatoid arthritis and nerve conditions like sciatica are more difficult. This is especially true of the latter which the malingerer can easily copy. In reality the chief problem is the matter of distinguishing real from simulated conditions. In the cases of real rheumatism the hope lies in combating the problem in the early stages. Mester stresses the need of early hospitalization and then warns against early discharge. Two principles are fundamental, namely, accurate diagnosis and adequate treatment by specialists.

*Psychotherapy.*—Wetherby<sup>334</sup> states:

This [psychotherapy] may be important in many individuals and is a form of therapy unintentionally given with any planned system of treatment. The encouragement of the patient and a hopeful outlook may be factors of great therapeutic

329. Payr, E.: Treatment and Restoration of Totally Crippled Hands in Severe Rheumatoid Arthritis, *Arch. f. klin. Chir.* **200**:527-545, 1940.

330. Magnuson, P. B.: Surgical Treatment of Degenerative Arthritis, *Surg., Gynec. & Obst.* **73**:1-9 (July) 1941.

331. Royle, N. D.: Operative Treatment of Chronic Sacroiliac Arthritis, *M. J. Australia* **2**:421 (Oct. 11) 1941.

332. Royle, N. D.: New Operation for Fixation of Sacroiliac Joint, *Australian & New Zealand J. Surg.* **5**:160 (Oct.) 1935.

333. Mester, A. J.: Rational Campaign Against Rheumatism in the Army, *J. Roy. Army M. Corps* **77**:24-28 (July) 1941.

334. Wetherby, M.: Therapeutic Procedures in Chronic Rheumatoid Disease, *Journal-Lancet* **61**:414-417 (Oct.) 1941.

significance. Faith healing and practices closely allied to them have seemingly benefitted many individuals with chronic rheumatoid disease probably because many patients have exaggerated their complaints out of proportion to the underlying disease process.

#### IX. INFANTILE PARALYSIS

*General Considerations.*—During the year of 1941 there was a definite increase of interest manifested by both laymen and members of the medical profession in infantile paralysis with regard to epidemiologic study, prevention, research and early care of patients. The incidence of the disease was generally higher over the whole country than in 1940 and reached epidemic form in many states and communities in the South, the East and the Middle West. The newspaper and magazine publicity given the work of the Australian nurse, Sister Elizabeth Kenny, who is sponsored by the National Foundation for Infantile Paralysis, has brought more and more inquiries to the physician regarding the value and the merits of this early form of therapy. Many encouraging reports were given at medical meetings during the latter part of the year on the use of the Kenny treatment, but few published reports are available in the literature. There is no doubt that the trend which started in 1940 away from absolute, continuous and rigid immobilization of the joints of the extremities in the acute stage of infantile paralysis has increased.

One of the most outstanding contributions from the epidemiologic viewpoint is that of the isolation of the virus from flies. There have been continued reports of the isolation of the virus from the gastrointestinal tract and from sewage, which was first reported in the literature of 1940. Another outstanding contribution reported from two or more sources and confirmed experimentally is that the patient who has had tonsillectomy is more susceptible to the disease than one who has not had this operation, the bulbar form being by far the most common.

*Epidemiologic Study.*—Trask and Paul,<sup>335</sup> studying the fecal material from patients with infantile paralysis, conclude that the evidence is yet not sufficient to permit the statement that the presence of poliomyelitic virus in sewage is a direct or even an indirect link in the chain which usually, or even occasionally, leads this infectious agent from one person to another. They further state that until more knowledge is available on this complex subject it seems unwise for health officers to introduce new methods of control.

Paul and Trask<sup>336</sup> believe that the poliomyelitis virus is probably transmitted from one person to another by a number of different channels.

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335. Trask, J. D., and Paul, J. R.: Observations on Fecal Examinations in Poliomyelitis, *Am. J. Pub. Health* **31**:239-244 (March) 1941.

336. Paul, J. R., and Trask, J. D.: Virus of Poliomyelitis in Stools and Sewage, *J. A. M. A.* **116**:493-497 (Feb. 8) 1941.

They are of the opinion that many infected persons may become convalescent carriers in the first few weeks of their recovery and may even become transient "healthy" carriers. Theoretically there may be other channels in which contaminated food, milk and water or conceivably insects, mammals and birds play a part. The authors feel definitely that water courses polluted with sewage may enter into the transmission of the disease.

[ED. NOTE: These observations are certainly most timely and pertinent to the subject and may be leading to the complete solution of the epidemiologic problem of the disease.]

Paul<sup>337</sup> further states that the real epidemiologic situation may be and is likely to be a complex, conditioned largely by summer weather and aided by rural environment. He believes that the nasopharyngeal portal of entry is unusual in human beings. [ED. NOTE: There is no doubt that the investigations of all workers in this field are pointing away from the nasopharynx and toward the gastrointestinal tract as the portal of entry.]

Sabin and Ward<sup>338</sup> report the case of a woman laboratory worker aged 35 in whom poliomyelitis developed, most likely contracted in the laboratory in which she was working with the virus.

Perkins<sup>339</sup> reports an epidemic of poliomyelitis in Minnesota in 1930 in which there was a definite radial spread of the disease from a central focus in a rural area. Instances are given of the apparent spread through person to person contact. He presents data which suggest possibly that on infection with the poliomyelitis virus male patients are more apt to have involvement of the nervous system and female patients are more apt to experience subclinical attacks. [ED. NOTE: This is an interesting observation, but the statistics on cases in epidemics do not show that male persons are any more often affected than female persons.]

*Causation.*—Piszczeck and others<sup>340</sup> report on a small epidemic in Cook County, Ill. They found the virus in the stools of 6 of 38 contacts; on the other hand, there was none found in 14 control specimens of normal residents in the community. The virus was found in the stools of 2 presumably healthy children who were in contact with adult mem-

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337. Paul, J. R.: Poliomyelitis, *Bull. New York Acad. Med.* **17**:259-267 (April) 1941.

338. Sabin, A. B., and Ward, R.: Natural History of Human Poliomyelitis: Distribution of Virus in Nervous and Non-Nervous Tissues, *J. Exper. Med.* **73**:771-793 (June) 1941.

339. Perkins, J. E.: Apparent Spread of Poliomyelitis Through Four Families, *Minnesota Med.* **24**:924 (Nov.) 1941.

340. Piszczeck, E. A.; Shaughnessy, H. J.; Zichis, J., and Levinson, S. O.: Acute Anterior Poliomyelitis: Study of Outbreak in West Suburban Cook County Illinois; Preliminary Report, *J. A. M. A.* **117**:1962-1965 (Dec. 6) 1941.



bers of their families who became ill with poliomyelitis. The virus was isolated from a presumably healthy person two months after his contact with persons who became ill with poliomyelitis and one month after contact with his father, who died of poliomyelitis.

Sabin and Ward <sup>341</sup> report investigative studies on the elimination of virus in patients with paralytic poliomyelitis during the first two weeks of the disease as follows: 1. The nasal secretions collected from 22 patients and the saliva and oral secretions expectorated by 20 patients failed to yield a virus. 2. In 10 of these patients the virus was isolated from single specimens of the lower part of the intestinal tract. 3. No virus was found in large amounts of urine obtained from 12 of these patients. 4. Virus was found in 50 per cent of 58 children under 8 years of age and from only 12 per cent of 60 older persons. [ED. NOTE: These statistics are certainly most interesting and are of extreme significance in the study of this disease.]

Sabin and Ward <sup>342</sup> isolated the virus from 5 of 16 flies caught in different sections of Atlanta, Ga., and Cleveland during outbreaks. Similar observations had previously been made by Paul and Trask in two rural areas in Connecticut and Alabama. This evidence certainly suggests that the contamination may have been picked up by the flies in the feces in open privies and certainly gives strong evidence for this mode of transmission of the disease.

Sabin <sup>343</sup> writes that the virus may continue to multiply in the alimentary tract long after the disappearance of the clinical signs of the disease; this is evident from the fact that in some instances the virus has been found to be excreted in the stools for weeks and months after clinical recovery. One instance is recorded in which the virus was found four months after a mild illness of two days' duration.

Fischer, Stillerman and Marks <sup>344</sup> report a high incidence of the bulbar form of infantile paralysis among the patients who had their tonsils and adenoids removed a short time prior to the illness. This was confirmed in the Toronto epidemic of 1937 among the children from 3 to 12 years of age. The authors cite the work of Sabin in which he has shown experimentally in monkeys that the injection of a moderate amount of virus into the tonsillopharyngeal region produced

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341. Sabin, A. B., and Ward, R.: Natural History of Human Poliomyelitis: Elimination of Virus, *J. Exper. Med.* **74**:519-529 (Dec.) 1941.

342. Sabin, A. B., and Ward, R.: Nature of Nonparalytic and Transitory Paralytic Poliomyelitis in Rhesus Monkeys Inoculated with Human Virus, *J. Exper. Med.* **73**:757-770 (June) 1941.

343. Sabin, A. B.: Olfactory Bulbs in Human Poliomyelitis, *Am. J. Dis. Child.* **60**:1313-1318 (Dec.) 1940.

344. Fischer, A. E.; Stillerman, M., and Marks, H. H.: Relation of Tonsillectomy and of Adenoidectomy to Incidence of Poliomyelitis with Special Reference to Bulbar Form, *Am. J. Dis. Child.* **61**:305-321 (Feb.) 1941.

poliomyelitis with involvement of the nuclei of the cranial nerves in 13 of 16 monkeys, while there was involvement of these structures in only 15 of 250 monkeys in which the disease developed after nasal instillation of virus. Sabin concludes that in most of the monkeys the virus entered and reached the nuclei of the cranial nerves along the nerves supplying the tonsillopharyngeal region. Fischer, Stillerman and Marks further conclude that the incidence of the bulbar form of infantile paralysis is twice as great in those patients whose tonsils have been removed at any time previously as in those with tonsils intact. Also cited in this article is a publication of Top and Vaughan reporting on an outbreak in Detroit in 1939 in which bulbar paralysis developed in 27 per cent of patients with their tonsils previously removed as against 4.2 per cent of those with their tonsils intact. In the 23 fatal cases in this epidemic, 20 patients, or 87 per cent, had tonsillectomy performed previous to the onset of the disease. [ED. NOTE: These figures are certainly most significant in the epidemiologic study of the disease.]

Krill and Toomey,<sup>345</sup> in writing on the part which tonsils play in poliomyelitis, conclude that poliomyelitis virus may have been present at the time of the operation in the throats of the children on whom they operated or that the virus may have been introduced after the operation. In the 5 cases which they report they suspect that the virus was not present in the throats when the tonsils and the adenoids were removed and that the virus was introduced later.

Duggan<sup>346</sup> states that it is his belief the pathologic and clinical evidence indicates that poliomyelitis may be due to a histamine-like body, that this body is a product of the body's own cells and that it may be produced by cold or as a result of antigen-antibody combination secondary to infection of the upper part of the respiratory tract. Allergy rather than immunity results. [ED. NOTE: This is a rather interesting observation, but it certainly needs further proof before it can be accepted.]

In his usual thorough way Toomey<sup>347</sup> concludes after a critical review of poliomyelitis that the following events are epochal in the progress of research on the disease in the past forty years: (1) the isolation of the virus from the human being and its transference to monkeys; (2) the demonstration of virus-neutralizing antibodies in the blood serums of convalescent patients with poliomyelitis; (3) the evaluation of the pathologic nature of the disease and the acceptance of the conception that nerve cells are destroyed first and that other

345. Krill, C. E., and Toomey, J. A.: Multiple Cases of Tonsillectomy and Poliomyelitis, *J. A. M. A.* **117**:1013 (Sept. 20) 1941.

346. Duggan, W. F.: Anterior Poliomyelitis: Manifestation of Acute Tissue Anoxia, *New York State J. Med.* **40**:1780-1787 (Dec. 15) 1940.

347. Toomey, J. A.: Poliomyelitis: Critical Review, *J. Pediat.* **19**:103-130 (July) 1941.

phenomena follow; (4) the demonstration that the virus spreads along neurons to the central nervous system; (5) the discovery that the virus can be acclimated to some smaller laboratory animals, and (6) the fact that the virus can be easily isolated from the stools of patients who have had the disease.

*Pathologic Characteristics.*—Peers,<sup>348</sup> comparing the lesions produced in the brain of man and monkey with a Lansing strain of virus, concludes that the lesions in the human brain agree in all essential details of type and distribution with those in a number of other brains from patients with poliomyelitis being studied in the laboratory. It was thought that generally the disease in the brain infected with the Lansing strain seemed anatomically rather less severe than that observed in other human specimens. The pattern of the fully developed disease was essentially identical in man and monkey, though the route of inoculation was obviously different.

Hipps,<sup>349</sup> reporting on his pathologic studies of muscle tissue in cases of anterior poliomyelitis, has certainly made a most worth while contribution to this part of the subject. He studied sections of various muscles during different stages of the disease. Gross pathologic examination of the muscles showed atrophy, degeneration and fibrous and fatty tissue replacement. There were zones of fibrofatty degeneration with good muscle above and below. The fatty change was nearly always the greatest near the musculotendinous junction. The muscles would not contract when pinched. They had no elasticity; they would stretch but when stretched would not return to their former length. These muscles were usually graded 0 on clinical examinations. The author is of the opinion that the results of physical therapy during his experience during the past fifteen years were definitely disappointing and that nature had more to do with the return of muscle power than physical therapists. He concludes by speculating on the possibility of improving muscle power by taking small strips of fascia lata and using these as mattress sutures to go between the belly of a good muscle across the fatty zone to the tendon below. He also brings up the question of injecting a sclerosing solution into this fatty zone between the good muscle and the tendon in order to form a strong fibrous mass which would effectively transmit the pull of the good segment above. [Ed. NOTE: This is an interesting and important pathologic study.]

Sabin and Ward<sup>338</sup> conclude that the pattern of virus distribution in human poliomyelitis points to almost the entire alimentary tract as a primary site of attack by the virus and contains no support for the

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348. Peers, J. H.: Poliomyelitis Induced by Lansing Strain of Virus: Comparison of Lesions in Man and in Monkeys, *Arch. Path.* **32**:928-938 (Dec.) 1941.

349. Hipps, H. E.: Muscle Pathology in Anterior Poliomyelitis in Relation to Function, *South. M. J.* **34**:135-146 (Feb.) 1941.

concepts involving either the olfactory pathway or the respiratory tract. The demonstration of virus in the abdominal sympathetic ganglions of 1 patient is significant in suggesting one of the possible routes of virus progression in certain instances. Pathologic studies on a large number of tissues obtained from patients who died have revealed that the virus is predominantly distributed in certain regions of the nervous system and in the alimentary tract.

*Experimental.*—Bodian and Howe<sup>350</sup> report on experimental work in which successive interruption of the nerve fibers of the sciatic nerve was performed by transection or freezing at intervals of two or three weeks at least three times. They found that the anatomically intact nerve fibers of the central stump as well as the incompletely regenerated fibers in the peripheral stump are rendered incapable of transmitting the poliomyelitis virus to the central nervous system. When a considerable number of fibers have completed their regeneration, however, that is, after at least two months have elapsed following the last nerve fiber interruption, inoculation of the central stump results in poliomyelitis. They conclude that the metabolic changes induced in neurons or their axons prevent infection by inoculation of the nerve central to the points of interruption, even when the virus of poliomyelitis is placed in direct contact with every axon. It is therefore highly probable that the axon protoplasm is the active transmitter of the virus in the nerve. When this protoplasm is sufficiently altered in its metabolism by the successive distal injuries and the resulting regenerative efforts, it is definitely refractory to the virus.

Sabin and Ward<sup>342</sup> write on the nature of nonparalytic and transitory paralytic poliomyelitis in monkeys inoculated with human virus. The term "nonparalytic poliomyelitis" has been used with reference to human beings to designate those who in addition to having the normal signs and symptoms of infantile paralysis, starting with headache, fever, vomiting and sore throat, have stiffness of the neck and the back, pleocytosis, tremor and other signs and symptoms of preparalytic poliomyelitis but in whom paralysis never develops. These patients show the virus in the stools. The authors have demonstrated the nonparalytic form in monkeys. In this infection there is a destruction of an appreciable number of nerve cells in the spinal cord; in the experiments, however, there was a failure of the process to progress which the authors feel was due to equilibrium between the host and the virus. The transitory character of the paralysis in some monkeys may have depended in part on the fact that apparently normal function can be carried on with less than the normal number of nerve cells and on the possibility

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350. Bodian, D., and Howe, H. A.: Experimental Studies on Intraneural Spread of Poliomyelitis Virus, *Bull. Johns Hopkins Hosp.* 68:248-267 (March) 1941.

that not all nerve cells attacked by poliomyelitis virus are irreversibly damaged. [ED. NOTE: This is another interesting study which may explain the absence of paralysis in patients associated with epidemics who have all the other signs and symptoms of the disease.]

Trask and Paul <sup>351</sup> have demonstrated that the green African monkey can be infected with the poliomyelitis virus as well as the Indian or rhesus monkey. This is the first time that monkeys other than rhesus monkeys have been infected.

*Clinical Findings.*—McDaniel <sup>352</sup> reports some interesting facts about the epidemic in South Carolina in 1939. The white and the Negro races were apparently equally susceptible. Eighty per cent of the cases in one county and 95 per cent of the cases in the other counties in the state were of the paralytic form. There were 35 deaths (7.9 per cent) in the total epidemic. The incidence of the epidemic extended over a six months' period from April to September. In this epidemic virus was recovered from sewage for the first time, and the cotton rat was able to be infected with the virus.

Plastridge <sup>353</sup> points out the dangers of habit limps in patients with infantile paralysis and points out some methods of prevention. Supervised instructed walking should make the gait smooth, steady and inconspicuous, make the gait as rapid as possible, with safety to the person and to the weakened muscles and make the walking not merely an expedient means of locomotion but a constant corrective training toward normal walking. [ED. NOTE: This is a valuable contribution. More attention should be paid to this by physical therapists and orthopedic surgeons. There is no doubt that a great many of the unsightly gaits of infantile paralysis could be prevented if more attention were paid to the early stages of walking after the paralysis.]

Kleinberg and Horwitz <sup>354</sup> made a study of the obstetric experiences of women who have had infantile paralysis. Their material consisted of 243 paralyzed women. They call attention to the following four types of deformity of the pelvis: (1) lateral pelvic obliquity; (2) increased anterior pelvic tilt with exaggerated lumbar lordosis; (3) anteroposterior axis deviation or rotation about a longitudinal axis, and (4) rotation of one innominate bone on the other innominate bone about a transverse axis, or torsional deformity. They conclude that a normal or

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351. Trask, J. D., and Paul, J. R.: Experimental Poliomyelitis in *Circopithecus Aethiops Sabaeus* (Green African Monkey) by Oral and Other Routes, *J. Exper. Med.* **73**:453-459 (April) 1941.

352. McDaniel, G. E.: Preliminary Discussion of Poliomyelitis in South Carolina in 1939, *J. South Carolina M. A.* **36**:331-336 (Dec.) 1940.

353. Plastridge, A. L.: Gaits, *Physiotherapy Rev.* **21**:24-29 (Jan.-Feb.) 1941.

354. Kleinberg, S., and Horwitz, T.: Obstetric Experiences of Women Paralyzed by Acute Anterior Poliomyelitis (with Special Reference to Pelvic Deformities), *Surg., Gynec. & Obst.* **72**:58-69 (Jan.) 1941.

uneventful pregnancy and labor with normal offspring is to be anticipated for these patients and that there is no indication for the interruption of the pregnancy at any stage.

Boyd<sup>355</sup> reports the presence of renal calculi in bedridden patients with poliomyelitis. He feels that the patient's position should be changed frequently and as completely as possible and that the patient should lie on the abdomen an hour or two at a time every day, beginning as soon as his paralysis and his general condition will permit. This condition is reported in 3 patients with infantile paralysis. [ED. NOTE: This is a sensible suggestion and should be carried out in every clinic.]

*Nonoperative Treatment.*—Levinson and Wolf<sup>356</sup> report on the use of immune serum in the treatment of infantile paralysis. They have used this serum extensively for the last ten years and feel that their results are encouraging. It has been used on 400 patients in the preparalytic stage, and the authors conclude that the incidence of moderate paralysis in this group is 4 per cent and that it is rare for severe paralysis to appear if serum treatment is started early in the disease. They believe that if the serum is given to paralyzed patients during the acute stage with the paralysis spreading that it may have some effect in checking the progression of the paralysis. They present no control untreated group for comparison. [ED. NOTE: Poliomyelitis immune serum is generally thought now to have little value in spite of this report to the contrary.]

Irwin,<sup>357</sup> writing on the early orthopedic care of the patient with poliomyelitis, gives his impressions of what has been considered the orthodox care during this stage, namely, that exercises should not be started until the improvement from immobilization ceases and that when these exercises are started they are best done in a warm water pool. This should be continued for three or four months before weight bearing is allowed if paralysis is in the legs. The author emphasizes the importance of complete rest during this early convalescent stage and that the exercises increase the muscle power by hypertrophy of the muscle tissue.

Hipps<sup>358</sup> reports on the care of 88 patients treated in the Crippled Children Hospital, Marlin, Tex., over a period of two and a half years.

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355. Boyd, M. L.: The Formation of Renal Calculi in Bedridden Patients, J. A. M. A. **116**:2245-2247 (May 17) 1941; The Significance of Sensory Paralysis in Poliomyelitis Patients in Whom Renal Calculi Develop, J. Urol. **45**:647-651 (May) 1941.

356. Levinson, S. O., and Wolf, A. M.: Human Serum: Its Application in Medicine, M. Clin. North America **25**:219-243 (Jan.) 1941.

357. Irwin, C. E.: Early Orthopedic Care in Poliomyelitis, J. A. M. A. **117**:280-282 (July 26) 1941.

358. Hipps, H. E.: Muscle Behavior Following Infantile Paralysis, Am. J. Surg. **53**:314-318 (Aug.) 1941.

In some of these cases the condition was in an early stage, and in some it was in a late stage. The author concludes that muscles long paralyzed lost strength much more often than they gained strength if treated in a relaxed position for six to twelve weeks; that muscles which were graded zero, trace or poor and had been paralyzed as long as three months showed no appreciable gain on physical therapy treatment; that muscles which were graded poor plus, fair and good showed a considerable and justifiable improvement with physical therapy; that the age group 6 to 16 years showed a greater improvement than younger or older groups, and that the patients who received early careful physical therapy showed much better muscle recovery than those treated otherwise. [ED. NOTE: This is an interesting study, but the number of cases is too small to make it of much value.]

Over a four year period McCarroll and Crego<sup>359</sup> studied 160 cases of recent infantile paralysis treated with various types of treatment. They conclude that since the type of early treatment has little or no effect on the course of the disease this does not alter the degree of residual paralysis which is seen. They believe that the orthopedic measures probably alter little, if at all, the course of the disease and that the residual involvement is primarily dependent on the degree of initial paralysis and the amount of actual destruction which has taken place in the cells of the anterior horn. They further believe that immobilization and protection are indicated for the comfort of the patient during the acute stage, the prevention of deformities and the prevention of stretch paralysis in the involved muscles. [ED. NOTE: This report has caused a great deal of comment and definitely contraindicates a great deal of prolonged physical therapy.]

Cole and Knapp<sup>360</sup> give the first report on the patients treated by Sister Kenny herself at the Minneapolis General Hospital and under the direction of the orthopedic and physical therapy departments of the University of Minnesota Medical School. In this report they simply give impressions. Since this time a great many accurate studies have been reported from this clinic. They conclude that certainly harm has not resulted to any of the observed patients under Miss Kenny's care from the abandonment of immobilization.

[ED. NOTE: There is certainly nothing in recent years that has caused more comment, favorable and unfavorable, on any one orthopedic subject than the principles as laid down for the early care of the patient

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359. McCarroll, H. R., and Crego, C. H., Jr.: *Evaluation of Physiotherapy in Early Treatment of Anterior Poliomyelitis*, J. Bone & Joint Surg. **23**:851-861 (Oct.) 1941.

360. Cole, W. H., and Knapp, M. E.: *Kenny Treatment of Infantile Paralysis: Preliminary Report*, J. A. M. A. **116**:2577-2580 (June 7) 1941.

with poliomyelitis by Elizabeth Kenny. Most observers who have watched her work and studied her methods are of the opinion that the results obtained are better than those obtained with the present orthodox method of care. No sound scientific reason which has been generally accepted has been given to explain these results. Many odd statements have been made by scientific persons without adequate basis or explanation. There is no doubt that a great deal of good will come from the discussions of this treatment and that our present orthodox methods are going to be altered to a considerable extent in the next few years. The time, the expense and the special training necessary for the workers employing the Kenny method may make the universal application of this treatment an impossibility for some time to come.]

Wilson<sup>361</sup> reports on the value of respirators in the treatment of poliomyelitis. Of 331 patients with infantile paralysis treated in respirators 150, or 45 per cent, died. In the 150 fatal cases 127 were patients reported as having the bulbar form of the disease or as having difficulty in swallowing. Of 204 patients with bulbar poliomyelitis 127 died—a mortality rate of 67 per cent; of the 127 patients with non-bulbar poliomyelitis 23 died—a mortality rate of 19 per cent. Many of the patients who died were in the respirators only a short time and probably could not have been expected to be materially helped. The impressions received from this article are that the use of a respirator for poliomyelitis is generally disappointing and that experience with this piece of apparatus certainly does not realize the high expectations for saving lives which were originally entertained. [ED. NOTE: It is the opinion of one of us (A. R. S.) that these conclusions are exactly right. If the opinion of Sister Kenny about respirators is correct, there will be no further need for them.]

*Operative Treatment.*—Eaton<sup>362</sup> reports the results of abdominal stabilization in the treatment of infantile paralysis. He found that in only 25 per cent of the cases in a small series was there increased power in the partially paralyzed abdominal wall muscles; that it is true that in 50 per cent of the cases there was marked improvement in the stabilization of the trunk on the pelvis; that in the presence of a developing scoliosis the operation appeared to be effective in arresting the progress of the deformity, and that the most striking benefit has been the patient's improvement in general physical well-being, the broadening of the activities, the increase of endurance and the lessened tendency to fatigue.

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361. Wilson, J. L.: Symposium on Poliomyelitis: Use of Respirator, J. A. M. A. **117**:278-279 (July 26) 1941.

362. Eaton, G. O.: Results of Abdominal Stabilization in Poliomyelitis, South. M. J. **34**:443-445 (April) 1941.



X. NEUROMUSCULAR DISORDERS, EXCLUSIVE OF INFANTILE  
PARALYSIS

*Neurologic Injuries of the Spine.*—In the past year much has appeared in the literature concerning injuries of the spine and the peripheral nerves. This is probably accounted for in part by the war. Harley<sup>363</sup> describes the various types of war injuries and wounds of the cord and the cauda equina. Dittrich<sup>364</sup> brings out the importance of damage to the epidural fat in producing neural symptoms in bullet wounds of the spine. Antonucci<sup>365</sup> describes the types of wounds and injuries of the cord and spinal nerves associated with vertebral injuries, and Gowlland,<sup>366</sup> the after-treatment of paraplegia in cases of wounds of the spine. Two articles, those by Jakob and associates<sup>367</sup> and Kankat,<sup>368</sup> describe complications of injuries due to compression of the spinal cord, such as painful spastic paraplegia and paralysis of the bladder and the rectum.

*Injuries to the Peripheral Nerves.*—With regard to the peripheral nerves attention is drawn to almost all of the joints in the body and the nerve injuries complicating wounds and other injuries of these joints. Hyslop<sup>369</sup> describes the complications of ankle sprain, and Isenschmid and Rieben<sup>370</sup> describe the sciatic lesions in cases of traumatic dislocation of the hip. Thompson<sup>371</sup> discusses paralysis of the serratus muscles complicating dislocation of the shoulder, and Dieulafé<sup>372</sup> paralysis of the median nerve complicating supracondylar fractures of the

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363. Harley, H. R.: Notes on War Injuries of Spinal Cord and Cauda Equina, *Guy's Hosp. Gaz.* **55**:41-43 (Feb. 22) 1941.

364. Dittrich, R. J.: Spinal Injury (Bullet Wound): Role of Epidural Fat in Producing Neural Symptoms; Report of Two Cases, *J. Kansas M. Soc.* **42**:65-69 (Feb.) 1941.

365. Antonucci, C.: Lesions of Spinal Cord and of Spinal Nerve Roots in Vertebral Injuries, *Arch. ed atti d. Soc. ital. di chir.* **43**:153-296, 1937.

366. Gowlland, E. L.: After Treatment of Paraplegic Patients Following Injuries to Spine, *Brit. M. J.* **1**:814-815 (May 31) 1941.

367. Jakob, C.; Prini, I.; Riedel, C., and Thenon, J.: Painful Spastic Paraplegia Due to Compression of Lower Dorsal Spinal Cord by Dural Psammoendelioma: Case with Improvement After Surgical Therapy, *Semana méd.* **2**:1387-1394 (Dec. 19) 1940.

368. Kankat, C. T.: Compression of Spinal Cord Due to Old Spinal Fracture: Paraplegia and Paralysis of Bladder and Rectum: Results of Surgical Intervention, *Türk tib cem. mec.* **6**:338-350, 1940.

369. Hyslop, G. H.: Injuries to Deep and Superficial Peroneal Nerves Complicating Ankle Sprain, *Am. J. Surg.* **51**:436-438 (Feb.) 1941.

370. Isenschmid, R., and Rieben, G.: Lesions of Sciatic Nerve in Traumatic Dislocations of the Hip, *Schweiz. med. Wchnschr.* **71**:137-141 (Feb. 8) 1941.

371. Thompson, G. C. V.: Paralysis of Serratus Anterior Muscle Complicating Dislocation of Shoulder, *M. J. Australia* **1**:231-232 (Feb. 22) 1941.

372. Dieulafé, R.: Paralysis of Median Nerve After Supracondylar Fracture of the Humerus: Case, *Mém. Acad. de chir.* **66**:703-706 (Oct. 16-30) 1940.

humerus. DeRabinovich<sup>373</sup> calls attention to the late appearance of ulnar paralysis after injury or wounds about the elbow.

In connection with injuries of the peripheral nerves in general Deery<sup>374</sup> outlines a number of different operative procedures for repair of injuries to the peripheral nerves in a rather complete listing of methods. Rogers<sup>375</sup> shows good results which may be obtained by the treatment of injuries of the peripheral nerves with amnioplastin (dried and sterilized amniotic membrane). Platt<sup>376</sup> describes wounds and injuries of nerves in general in a symposium on the sequelae of war wounds.

An article by Homans<sup>377</sup> describes minor causalgia of different nerves following injuries and wounds, and Hurst<sup>378</sup> draws attention to hysterical contractures following injuries in war.

It may be seen, therefore, that there is a constantly increasing flow of material concerning the traumatic conditions of nerves; this will undoubtedly become further augmented in the coming year.

*Cerebral Palsy.*—In the field of cerebral palsy there is also a wider distribution of literature than previously. An article by Putnam<sup>379</sup> details a careful distinction between the neurologic aspects of spasticity and athetosis. Wolf,<sup>380</sup> in considering the therapy of hemiplegia both of cerebral palsy and poliomyelitis origin, points out that it is important to determine the presence of contractile muscle if any attempt to obtain return of power is expected to be made. Electrical reactions in patients with poliomyelitis will allow the selection of suitable subjects with reasonable certainty. The author feels that the use of long wave diathermy often brings about definite improvement in some of the cases in which the condition has been present a long time. Norfleet, Raney and Baker<sup>381</sup> discuss the major types of cerebral palsy, namely, spasticity,

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373. de Rabinovich: Late Ulnar Paralysis After Injury to the Elbow: Cases, *Rev. neurol. de Buenos Aires* **5**:122-131 (April-June) 1940.

374. Deery, E. M.: Injuries to Peripheral Nerves, *S. Clin. North America* **21**:469-483 (April) 1941.

375. Rogers, L.: Experiences in Treatment of Peripheral Nerve Injuries with Amnioplastin, *Brit. M. J.* **1**:587-589 (April 19) 1941.

376. Platt, H.: Symposium on Sequelae to War Wounds: Sequelae to Nerve Injuries, *M. Press* **205**:371-373 (May 7) 1941.

377. Homans, J.: Minor Causalgia Following Injuries and Wounds, *Ann. Surg.* **113**:932-941 (June) 1941.

378. Hurst, A.: Hysterical Contractures Following Injuries in War, *Clin. J.* **70**:29-40 (Feb.) 1941.

379. Putnam, T. J.: Neurologic Aspects of Spasticity and Athetosis, *New York State J. Med.* **41**:1822-1827 (Sept. 15) 1941.

380. Wolf, H. F.: Treatment of Fresh and Old Cases of Hemiplegia and Poliomyelitis by Physical Therapy, *M. Rec.* **153**:263-265 (April 16) 1941.

381. Norfleet, G. M.; Raney, R. B., and Baker, L. D.: Neurologic Orthopedic and Therapeutic Aspects of Cerebral Palsy, *North Carolina M. J.* **2**:236-242 (May) 1941.

athetosis, incoordination and tremor, and the pathologic changes and the physical differentiation of the types. They describe also the establishment of the cerebral palsy unit at the Duke University School of Medicine and outline briefly some of the principles of treatment. Gustafson and Garceau<sup>382</sup> have statisticized 185 cases of cerebral spastic paralysis and point out that the proper management of labor is a factor in the prevention of the condition. They feel that premature labor is the greatest single factor in the causation of cerebral palsy and conclude that many cases of cerebral spastic paralysis may occur when labor has been thoughtlessly managed. Boorstein<sup>383</sup> gives a summary of the general problem of the child with cerebral palsy both from the mental and from the physical point of view, concluding that the Binet-Simon method of intelligence testing is not entirely adequate and discussing to some extent the various causative factors. He points out the inadvisability of operation on patients with athetosis and states that operations should be limited exclusively to patients with spastic cerebral palsy. Brander<sup>384</sup> describes the heredity of congenital spastic hemiplegia, and Haldane,<sup>385</sup> partial sex linkage of recessive spastic paraplegia. Jakob and Scaravelli<sup>386</sup> describe deaf-mutism and familial spastic quadriplegia in 7 brothers and a sister. The three aforementioned articles are interesting because of their demonstration of the hereditary factors sometimes seen in certain types of spastic paralysis. Phelps<sup>387</sup> has presented a series of articles concerning different phases of the control of spastic paralysis. One article describes the differential characteristics; another, the rehabilitation; a third, factors influencing treatment, and the fourth, the correlation between physical therapy and occupational therapy in the treatment of the condition.

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382. Gustafson, G. W., and Garceau, G. J.: Cerebral Spastic Paralysis: Obstetric History of One Hundred and Eighty-Five Cases, *J. A. M. A.* **116**:374-377 (Feb. 1) 1941.

383. Boorstein, S. W.: Cerebral Palsy Child, *Arch. Pediat.* **58**:578-596 (Sept.) 1941.

384. Brander, T.: Heredity of Congenital Spastic Hemiplegias, *Acta pædiat.* (suppl. 1) **28**:114-122, 1940.

385. Haldane, J. B. S.: Partial Sex-Linkage of Recessive Spastic Paraplegia, *J. Genetics* **41**:141-147 (Jan.) 1941.

386. Jakob, C., and Scaravelli, A.: Idiocy, Deaf-mutism and Familial Spastic Quadriplegia in Seven Brothers and Sister, *Rev. neurol. de Buenos Aires* **5**:283-299 (Oct.-Dec.) 1940.

387. Phelps, W. M.: Differential Characteristics of Spasticity and Athetosis in Relation to Therapeutic Measures, *New York State J. Med.* **41**:1827-1831 (Sept. 15) 1941; Rehabilitation of Cerebral Palsy, *South. M. J.* **34**:770-776 (July) 1941; Factors Influencing Treatment of Cerebral Palsy, *Physiotherapy Rev.* **31**:136-138 (May-June) 1941; Correlation of Physical Therapy and Occupational Therapy in Cerebral Palsy, *Arch. Phys. Therapy* **22**:587-590 (Oct.) 1941.

*Brachial Plexus Paralysis.*—Ruhlin<sup>388</sup> presents a clinical study of obstetric paralysis and its relation to birth injury of the brachial plexus or the muscular, ligamentous and capsular apparatus around the shoulder joint. He feels that the disability is a common one; that the treatment is well standardized, and that gratifying results can be obtained in most cases. Finochietto and Dickmann<sup>389</sup> describe the traumatic lesions in the brachial plexus in adults and the technic of surgical treatment for them. Götze<sup>390</sup> describes lesions which have been found in peripheral nerve injuries of the brachial plexus. Kolodny<sup>391</sup> and Greiner<sup>392</sup> describe the causation of obstetric injuries and traction paralysis of the brachial plexus. Putti<sup>393</sup> describes the similarity between obstetric and poliomyelitis syndromes of the upper extremity and the surgical therapy to be used for some of these types. Lance<sup>394</sup> describes the so-called obstetric paralysis of the upper and lower extremities, which is not a brachial palsy in all cases but which may be a more generalized injury of the cord.

*Tabetic Arthropathies.*—Sashin<sup>395</sup> describes early tabetic arthropathy of the metatarsophalangeal joint of the great toe. He concludes that arthropathy is often the first sign of a tabetic process and that pain may definitely be present on motion in the early stages. Negative results of serologic tests do not rule out tabetic arthropathy. The earliest signs may be seen by roentgen examination. The author concludes that early diagnosis is most important in order that the joint may be protected and the development of an unstable and markedly deformed articulation prevented. Pomeranz and Rothberg<sup>396</sup> review 58 cases of tabetic arthropathy. The largest number of cases occurred

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388. Ruhlin, C. W.: Clinical Study of Obstetric Paralysis, J. Maine M. A. **32**:205-208 (Sept.) 1941.

389. Finochietto, R., and Dickmann, G. H.: Traumatic Lesions of the Brachial Plexus in Adults: Technic of Surgical Therapy, Arch. argent. de neurol. **23**:30-43 (July-Dec.) 1940.

390. Götze, W.: Lesions of the Brachial Plexus in Peripheral Nerve Injuries, Arch. f. Psychiat. **112**:469-473, 1940.

391. Kolodny, A.: Traction Paralysis of Brachial Plexus, Am. J. Surg. **51**:620-629 (March) 1941.

392. Greiner, K.: Hemiplegia in Infant Due to Obstetric Trauma: Case, Kinderärztl. Praxis **11**:378-380 (Dec.) 1940.

393. Putti, V.: Obstetric and Poliomyelitic Paralytic Syndromes of Upper Extremity: Surgical Therapy with Note on Physiopathology of Rotation of Forearm, Chir. d. org. di movimento **26**:215-229 (Nov.) 1940.

394. Lance: So-Called Obstetric Paralysis of Upper and Lower Extremities: Case, Bull. Soc. de pédiat. de Paris **37**:512-513, 1940.

395. Sashin, D.: Early Tabetic Arthropathy of Metatarsophalangeal Joint of Big Toe, Bull. Hosp. Joint Dis. **2**:105-110 (July) 1941.

396. Pomeranz, M. M., and Rothberg, A. S.: Review of Fifty-Eight Cases of Tabetic Arthropathy, Am. J. Syph., Gonorr. & Ven. Dis. **25**:103-119 (Jan) 1941.

in the fifth and sixth decades of life in white male patients. The knee joint was affected in many cases, and there was multiple involvement in 19 cases. The authors also conclude that roentgen examination provides the most reliable diagnostic aid and that serologic tests may not always be positive. Pain is found to be present early in cases of arthropathy. The authors do not feel that fusion or stabilization operations are advisable in view of the end results which they have seen.

*Meralgia Paraesthetica.*—Lee<sup>397</sup> describes meralgia paraesthetica as a compression of and tension on the lateral femoral cutaneous nerve as it passes under the inguinal ligament. He concludes that this is the cause since in instances in which neurolysis was performed there resulted a progressively favorable increase in the sensation of the skin. He describes the operative treatment for the condition in which the nerve is relocated in a slot in the ileum. In this way normal sensation can be restored to the skin. King<sup>398</sup> describes the treatment of meralgia paraesthetica by resection of the segment of the femoral cutaneous nerve when the condition has been resistant to conservative therapy. He states that a diagnostic aid is the injection of procaine hydrochloride into the nerve trunk in the upper part of the thigh with relief of pain. A method of treating the condition is the injection of absolute alcohol into the cut ends of the nerve after section to prevent the formation of a neuroma. The author feels that in many cases relief may be obtained by conservative treatment rather than by operation and that conservative treatment should be tried first in all cases.

*Myasthenia Gravis, Dystrophia Myotonica, Progressive Muscular Dystrophy and Other Conditions.*—An article by Blalock, Harvey, Ford and Lilienthal<sup>399</sup> describes the treatment of myasthenia gravis by removal of the thymus gland. This article is in the form of a preliminary report on the effects of the removal of the thymus on the course of myasthenia gravis. It is felt that the results are encouraging and that these suggest that the thymus is concerned with the genesis of myasthenia gravis. They also suggest that the thymus is a gland with an internal secretion and that it may have a definite function. Harvey and Masland<sup>400</sup> have described the muscle contractions which charac-

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397. Lee, F. C.: Osteoplastic Neurolysis Operation for Cure of Meralgia Paraesthetica, *Ann. Surg.* **113**:85-94 (Jan.) 1941.

398. King, B. B.: Meralgia Paraesthetica: Report of Five Cases, *Am. J. Surg.* **52**:364-368 (May) 1941.

399. Blalock, A.; Harvey, A. M.; Ford, F. R., and Lilienthal, J. L. J.: Treatment of Myasthenia Gravis by Removal of Thymus Gland: Preliminary Report, *J. A. M. A.* **117**:1529-1533 (Nov. 1) 1941.

400. Harvey, A. M., and Masland, R. L.: Electromyogram in Myasthenia Gravis, *Bull. Johns Hopkins Hosp.* **69**:1-13 (July) 1941.

teristically appear in the electromyogram in cases of myasthenia gravis. Boman<sup>401</sup> describes thymus changes seen in cases of myasthenia gravis.

Maybarduk and Levine<sup>402</sup> describe the atrophy seen in the bones and associated with progressive muscular dystrophy. They offer evidence that concentric osseous atrophy is a primary feature and is not secondary to disuse. They suggest that an endocrine disorder or a disturbance of the vegetative nervous system may be the source of these changes. Epstein and Abramson<sup>403</sup> also report interesting roentgen studies of patients with progressive muscular dystrophy which confirm some of the findings of Maybarduk and Levine. Lewis, Ravin and Lewis<sup>404</sup> discuss the excretion of creatine and creatinine and the effect of glycine administration on muscular dystrophy. They state that while the evidence is not sufficient for drawing complete conclusions it seems to augment the evidence that slight to moderate creatinuria which may be observed in cases of dystrophia myotonica is neither as constant nor as striking a finding as in cases of progressive muscular dystrophy and that the condition is less strongly affected by the administration of glycine than in cases of the latter disease. Milhorat,<sup>405</sup> in discussing the hereditary factors in the causation of muscular dystrophies, states that since the disease is associated with defective metabolism of creatine and creatinine it is possible that the factors causing creatinuria in childhood and infancy might be of importance in determining the early extensive distribution and rapid clinical progression of the process when the disease develops in the first decade of life.

Branch<sup>406</sup> divides pseudohypertrophic muscular dystrophy into the infantile and juvenile types. The infantile type shows the muscle to have a pale water-logged appearance with a degeneration of the individual fibers and profuse fibrous tissue between. The juvenile type presents more nearly normal muscle fibers, but there is an infiltration of fat between the fibers and there are fewer individual muscle fibers. A new regimen of treatment is described which includes the following measures: 1. Estrogenic substances are given to influence favorably the creatine-creatinine utilization and excretion. 2. Choline is given to

401. Boman, K.: Thymus Changes in Myasthenia Gravis, *Nord. med. (Hygiea)* **10**:1625-1634 (May 24) 1941.

402. Maybarduk, P. K., and Levine, M.: Osseous Atrophy Associated with Progressive Muscular Dystrophy, *Am. J. Dis. Child.* **61**:565-576 (March) 1941.

403. Epstein, B. S., and Abramson, J. L.: Roentgenologic Changes in Bones in Cases of Pseudohypertrophic Muscular Dystrophy, *Arch. Neurol. & Psychiat.* **46**:868-876 (Nov.) 1941.

404. Lewis, R. C., Jr.; Ravin, A., and Lewis, R. C.: Studies in Dystrophia Myotonica: Creatine and Creatinine Excretion, *J. Lab. & Clin. Med.* **26**:990-995 (March) 1941.

405. Milhorat, A. T.: Hereditary Factors in Muscular Dystrophies and Other Considerations, *Tr. Am. Neurol. A.* **66**:120-122, 1940.

406. Branch, H. E.: Progressive Pseudohypertrophic Muscular Dystrophy: New Regime of Treatment, *J. Michigan M. Soc.* **40**:814-822 (Oct.) 1941.

influence the metabolism and the deposition of fat. 3. Cow's or goat's milk is given to increase the magnesium content of the muscle. 4. An extract of the anterior lobe of the pituitary gland is given to hasten the growth of the patient to maturity.

The results of the treatment of 6 patients show that in 3 on the full regimen there was a marked increase in muscular power; in 2 there was definite improvement, and in 1 there was improvement until bilateral otitis media developed. These results are considered by the author to be encouraging.

Hauptmann and Thannhauser<sup>407</sup> report an apparently new hereditary familial disease in an article on muscular shortening and dystrophy. This condition affects only the muscular system and is not markedly progressive. It occurred in a family of French Canadians and was characterized by a short webbed neck with a normal roentgenogram of the cervical portion of the spine. There was also some evidence of shortening and weakening in many of the muscles. There were some features of progressive muscular dystrophy present.

*Paralysis, Traumatic or Occupational.*—Roger and Schachter<sup>408</sup> discuss peroneal and sciatic paralysis after gluteal injections of bismuth and present a case of paralysis of the external popliteal branch of the sciatic nerve. Guillain, Bourguignon and Corre<sup>409</sup> describe ulnar paralysis in bicyclers and report 4 cases. Ransohoff<sup>410</sup> describes peroneal paralysis caused by a cyst of the lateral meniscus of the knee joint. Hogan<sup>411</sup> reports multiple neuritis as a serum reaction with a discussion of 2 cases. He points out that this distinct clinical entity is a complication which may follow the use of serum therapy and should be more widely recognized. He states that it is important to know that it has a favorable prognosis.

*Vitamin Therapy for Neuromuscular Disorders.*—DeJong<sup>412</sup> writes concerning vitamin E in the treatment of amyotrophic lateral sclerosis.

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407. Hauptmann, A., and Thannhauser, S. J.: Muscular Shortening and Dystrophy: Heredofamilial Disease, *Arch. Neurol. & Psychiat.* **46**:654-664 (Oct.) 1941.

408. Roger, H.; Schachter, M., and Fournier, A.: Sciaticas After Intragluteal Injections of Bismuth: Case of Paralysis of External Popliteal Branch of Sciatic Nerve, *Medicina, Madrid* **9**:172-178 (March) 1941.

409. Guillain, G.; Bourguignon, G., and Corre: Ulnar Paralysis of Cyclists: Report of Four Cases, *Bull. et mém. Soc. méd. d. hôp. de Paris* **56**:489-492 (Sept. 24) 1940.

410. Ransohoff, N. S.: Cyst of Lateral Meniscus Causing Peroneal Nerve Palsy, *Bull. Hosp. Joint Dis.* **2**:69-71 (April) 1941.

411. Hogan, B. W.: Neuritis as Serum Reaction: Report of Two Cases, *U. S. Nav. M. Bull.* **39**:403-408 (July) 1941.

412. DeJong, R. N.: Vitamin E and Alpha-Tocopherol Therapy of Neuromuscular and Muscular Disorders, *Arch. Neurol. & Psychiat.* **46**:1068-1075 (Dec.) 1941.

He states that no outstanding clinical response can be demonstrated either in cases of amyotrophic lateral sclerosis or in cases of progressive spinal muscular atrophy with bulbar palsy. The only changes of significance are a slight decrease in the fibrillary tremors, a feeling of well-being and a slight gain in weight in some patients. There may also be a subjective increase in muscular strength in the early course of the therapy. The author feels that the progress of the disease may have been retarded or arrested in certain instances but that this is purely speculative since the pathologic process advances with varying speed in different people. Large doses of vitamin E, or alpha tocopherol, have no advantage over smaller doses. Eaton, Woltman and Butt<sup>413</sup> write of vitamin E and vitamin B<sub>6</sub> in the treatment of neuromuscular diseases. They found no conclusive evidence that vitamin E alone or in combination with vitamin B or other vitamins is of any benefit in the treatment of amyotrophic lateral sclerosis, progressive muscular atrophy or progressive muscular dystrophy. Meller<sup>414</sup> likewise has evaluated the use of vitamin E in the treatment of multiple sclerosis and progressive muscular atrophy and concludes that in 12 cases of multiple sclerosis no response to intensive therapy with vitamin E was found. However, in 14 cases of varying types of progressive muscular atrophy 3 patients apparently recovered; 7 showed definite improvement, and 4 failed to respond. The author points out that large doses over a long period of time are necessary; he observed no toxic symptoms attributable to the medication. Telford<sup>415</sup> describes the degeneration and the loss of nerve endings in the degenerated skeletal muscles of young vitamin E-deficient rats. Many of these writers are unable to explain the startling results seen in rats and the lack of any specific response to treatment with vitamin E in human beings. Hanisch<sup>416</sup> describes the successful use of a vitamin B complex preparation made from yeast and wheat germ in the treatment of myotonia congenita. In an extensive article on the nature of certain diseases of the voluntary muscles Gammon, Harvey and Masland<sup>417</sup> describe in great detail the relation of the various muscular diseases to the present use of biochemicals.

413. Eaton, L. M.; Woltman, H. W., and Butt, H. R.: Vitamins E and B in the Treatment of Neuromuscular Diseases, *Proc. Staff Meet., Mayo Clin.* **16**: 523-527 (Aug. 13) 1941.

414. Meller, R. L.: Evaluation of Vitamin E in Treatment of Multiple Sclerosis and Progressive Muscular Atrophies, *Journal-Lancet* **61**:471-478 (Dec.) 1941.

415. Telford, I. R.: Loss of Nerve Endings in Degenerated Skeletal Muscles of Young Vitamin E Deficient Rats, *Anat. Rec.* **81**:171-181 (Oct. 25) 1941.

416. Hanisch, P.: Successful Therapy of Oppenheim's Myotonia with Eugenzym (Vitamin B Preparation), *München. med. Wchnschr.* **88**:304-305 (March 14) 1941.

417. Gammon, G. D.; Harvey, A. M., and Masland, R. L.: On Nature of Certain Diseases of the Voluntary Muscles, *Biol. Symposia* **3**:291-330, 1941.



Oldberg<sup>418</sup> describes the different types of pain arising from various types of nerve lesions. First he presents a case of pain arising from an extramedullary intradural spinal tumor, then a second case of tabetic radiculitis, a third of postherpetic neuritis, a fourth of alcoholic-avitaminotic peripheral neuritis, a fifth of peripheral neurofibroma, a sixth of neuritis resulting from focal infection, a seventh of neuritis due to cervical rib and an eighth of pain caused by a protruded intervertebral disk.

These are fairly typical examples of specific types of pain, and the paper is an interesting and important description of the differences between these various syndromes.

*Surgical Technics.*—Finochietto and Dickmann<sup>419</sup> describe the technic for exposure in the lower half of the arm and the elbow of the radial nerve. This is a posterior route and appears to be a satisfactory exposure. Malan<sup>420</sup> describes the grafting of spinal cord or nerve in the process of repair for loss of peripheral nerve substance with satisfactory results.

#### XI. TUMORS OF BONE

*Experimental Work.*—To produce tumors experimentally Turner<sup>421</sup> implanted bakelite disks in 13 rats. In 4 of 9 rats living over twenty months fibrosarcomatous tumors developed about the disks. The bakelite disks probably served as another carcinogenic agent of low potency, and the development of tumor tissue may have been entirely due to chronic irritation.

Franseen, Aub and Simpson,<sup>422</sup> implanting methylchloranthine crystals resulting from the evaporation of colloidal thorium dioxide and radon seeds near the upper tibial epiphysis in rats, failed to produce osteogenic sarcomas but did produce fibrosarcomas, probably extraosseous with origin in muscle.

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418. Oldberg, E.: Pain Arising from Lesions of Nerves and Spinal Cord: Differential Diagnosis and Treatment, *M. Clin. North America* **25**:55-62 (Jan.) 1941.

419. Finochietto, R., and Dickmann, G. H.: Technic for Exposure of Radial Nerve in Lower Half of Arm and Elbow by Posterior Route, *Rev. de cir. de Buenos Aires* **19**:10-17 (Jan.) 1940.

420. Malan, R.: Results of Grafting Spinal Cord or Nerve in Process of Repair of Loss of Peripheral Nerve Substance: Experimental Study, *Arch. per le sc. med.* **70**:587-605 (Dec.) 1940.

421. Turner, F. C.: Sarcomas at Sites of Subcutaneously Implanted Disks in Rats, *J. Nat. Cancer Inst.* **2**:81-83 (Aug.) 1941.

422. Franseen, C. C.; Aub, J. C., and Simpson, C. L.: Experimental Production of Fibrosarcomas of Bone, *Cancer Research* **1**:393-396 (May) 1941.

In the field of experimental therapy Stark <sup>423</sup> has studied the effects of various ultraviolet light wavelengths on living sarcoma cells. She had noted that certain stages of spermatogenesis reacted to  $\lambda$  2,750 wavelength. Following her work on the rat sarcoma no. 39 from the Crocker Institute, she proves that there is no relation between the absorption and the lethal effect of light and that wavelengths shorter than  $\lambda$  2,573 are destructive and lethal in three seconds at  $\lambda$  2,300. She feels that the lethal effects of shorter wavelengths can probably be utilized in surface irradiation or that they can be generated within the cells by impregnation with some substance which under the action of still shorter wavelengths, such as roentgen rays, will cause the substance to emit the shorter ultraviolet waves. Such experiments have been started. [ED. NOTE: This work is interesting but rather technical and probably could be more appreciated if a similar series of experiments were run with roentgen rays of varying lengths.]

Blood chemistry with the determination of serum and tissue phosphatase still presents diagnostic aid of some value, but only when positive reactions are obtained. Woodard and Higinbotham <sup>424</sup> have determined a normal alkaline serum phosphatase content of 1.5 to 5 units for adults and 5 to 13 units for children. Their standard for the acid serum phosphatase is usually less than 5 per cent of the alkaline value. They conclude that benign tumors of bone produce much phosphatase which does not enter the circulation and some which does enter. They have shown that the phosphatase mechanism of tumors is inactivated by roentgen therapy when the dose is 4,000 r or greater. They have demonstrated that the giving of radioactive phosphorus by mouth will localize portions of the tumor containing the most phosphatase, and they feel that the changes in the phosphatase afford definite indication of the effect of roentgen therapy. These findings are of value only in those cases in which the serum phosphatase value is above normal.

Herger and Sauer <sup>425</sup> have studied the relation of the serum acid phosphatase value to the presence of metastasis from carcinoma of the prostate. They conclude that determination of the serum acid phos-

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423. Stark, M. B.: Effect of Various Ultraviolet Light Wave Lengths upon Living Sarcoma Cells, New York M. Coll. & Flower Hosp. Bull. **3**:358-371 (Dec.) 1940.

424. Woodard, H. Q., and Higinbotham, N. L.: Serum and Tissue Phosphatase Determinations as Aid in Evaluating Radiation Therapy, J. A. M. A. **116**:1621-1627 (April 12) 1941.

425. Herger, C. C., and Sauer, H. R.: Relationship of Serum Acid Phosphatase Determination to Presence of Metastases from Carcinoma of Prostate, J. Urol. **46**:286-302 (Aug.) 1941.

phatase is a valuable adjunct in the diagnosis of bone metastasis. If the determination gives a value of 4 to 6 units, metastasis is possible; if the value is over 6 units, metastasis is probable. The rapid progressive elevation of the acid serum phosphatase offers a bad prognostic sign.

*Classification.*—In 1941 the literature on bone tumors continued to contain various critical viewpoints on the classification of osteogenic tumors. Jacobson<sup>426</sup> in a critique on interrelationships of osteogenic tumors states that the present attitude is not logical in the consideration of the interrelationships of the tumors of the skeletal tissues. In this excellent article he outlines fourteen groups of bone tumors, giving somewhat in a visual way the tissues of origin from which are developed the benign and malignant bone tumors. The classification is as follows:

1. Periosteal fibroma. This is theoretically possible.
2. Periosteal fibrosarcoma. This is theoretically possible.
3. Central fibroma. This is presumably derived from the connective tissue of marrow.
4. Medullary fibrosarcoma. This probably occurs more frequently than is recognized; possibly it is often mistaken for osteolytic osteogenic sarcoma.
5. Lipoma and liposarcoma. The first is impossible to recognize; the second has been described.
6. Enchondroma. This probably is caused by failure of absorption of part of the cartilage growth plate.
7. Chondrosarcoma. The author believes that in all cases this tumor is derived from preexisting nonmalignant cartilage cells.
8. Ecchondrosis. This is presumably derived from perichondrium.
9. Cartilaginous exostosis. This is periosteal dysplasia in hereditary form. The single form may be traumatic. The author gives a long discussion.
10. Osteoma. This is the same as cartilaginous exostosis in membranous bones.
11. Osteoid osteoma. This is an endosteal neoplasm.
12. Osteogenic sarcoma. The chondroplastic type is rare and variable.
13. Giant cell tumor. The author feels that in all cases in which it is endosteal in origin it is related to the two classes just mentioned. It develops from osteoid osteoma through giant cell tumor to osteogenic sarcoma. Its development is dependent on the metabolic activity of the region in which it arises; this is low in the diaphysis and the epiphysis and high in the metaphysis. The more malignant developments are all composed of the same elements, viz., spindle cells, osteoblasts, osteoid, bone and giant cells.
14. Heterotopic bone tumors. These have the same potentialities as osteoplastic and chondroplastic tumors.

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426. Jacobson, S. A.: Critique on Interrelationships of Osteogenic Tumors, *Am. J. Cancer* 40:375-402 (Nov.) 1940.

*Roentgen Studies.*—In a study of growth in 200 children Sontag and Pyle<sup>427</sup> have made serial roentgenograms started at birth and repeated each three to six months up to 18 years of age. In this mass of roentgen material they have observed cystlike areas in the distal metaphyses of the femurs of children between the ages of 2 and 9 years. The average duration is twenty-nine months. These cysts are asymptomatic and disappear spontaneously. They are interpreted as the result of local removal of bone salts or as due to the inclusion of small groups of cartilage cells; on the other hand, they may be of the same pathologic nature as solitary cysts in origin, only they do not progress with their osteoclastic tendency. No biopsies have been done. This is altogether a clinical and roentgen study. [ED. NOTE: The authors should have excellent material for studies of bone growth.]

In a discussion on roentgenography in the diagnosis of bone tumors, Sutherland<sup>428</sup> presents two fundamental principles: First, with benign tumors of bone the continuity of the contour of the bone is retained. Second, with malignant tumors of bone there is dissolution of the contour shadow, and this applies to the soft tissue shadows as well. To these fundamentals there are three exceptions, namely, tumors of soft tissue, periosteal fibrosarcoma and Ewing's tumor. This is an elementary discussion of the roentgen differentiation of the various types of bone tumors and is of value particularly from the teaching standpoint.

*Benign Tumors of Bone.*—In the literature of the past year there are 2 additional case reports of osteoid osteoma, which has been previously described by Jaffe.

A tumor in the upper part of the tibia with a differential diagnosis of osteomyelitis, sclerosing osteitis of Garré or an osteoid osteoma is described as a Cabot case.<sup>429</sup> Exploration of this tumor with tissue study and negative cultures confirmed the diagnosis.

The second case was reported by Kleinberg.<sup>430</sup> The patient was a 24 year old man with a painful tumor of the femur in the midshaft in the cortical bone. This tumor existed for four years. At the end of two years the tumor was biopsied, and the diagnosis of osteomyelitis

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427. Sontag, L. W., and Pyle, S. I.: Appearance and Nature of Cyst-Like Areas in Distal Metaphyses of Children, *Am. J. Roentgenol.* **46**:185-188 (Aug.) 1941.

428. Sutherland, C. G.: Roentgenography in Diagnosis of Tumors of the Bone, *M. Clin. North America* **25**:1041-1065 (July) 1941.

429. Osteoid Osteoma of the Tibia, Cabot Case 27492, *New England J. Med.* **225**:920-922 (Dec. 4) 1941.

430. Kleinberg, S.: Osteoid Osteoma of Femur, *Am. J. Surg.* **53**:168-171 (July) 1941.

was made. Two years later a second exploration was done; the tumor was removed and diagnosed pathologically by Jaffe as an osteoid osteoma.

The literature of the past year on chondroma consists chiefly of individual case reports. Pearce and Collins<sup>431</sup> report a tumor in the shaft of the ulna showing rapid growth. On microscopic examination it was not definitely malignant, though the clinical course was definitely strongly suggestive. [ED. NOTE: One of us (R. D. S.) interprets this tumor as probably an enchondroma activated by trauma.]

An interesting case is reported by Carter and Heitzman.<sup>432</sup> The diagnosis was Ollier's dyschondroplasia with multiple chondromas of all bones of one lower extremity and the pelvis. This was treated by disarticulation at the hip joint. There has been no evidence of malignant growth in these sections. This case is well reported with splendid photographs and photomicrographs.

Mayer<sup>433</sup> reports a case in which excision of chondroma of the ribs was followed three years later by recurrence which showed on clinical and microscopic examination the signs typical of chondrosarcoma. The tumor was treated by wide excision of the anterior chest wall including the pleura and an immediate transplantation of fascia lata. There had been no recurrence of the tumor five years from the time of the second excision.

*Giant Cell Tumor.*—In a study of giant cell tumor Lichtenstein and Jaffe<sup>434</sup> express the firm opinion that the diagnosis of giant cell tumor is made too frequently, and they regard the numerous variants as being in reality incorrect diagnoses. In their opinion the giant cell tumor of bone is a neoplasm of definite kind, arising apparently from the undifferentiated supporting tissue of the marrow and clearly delimitable on the basis of the cytologic details. Essentially it is composed of more or less vascularized network of spindle-shaped or ovoid stromal cells in multinuclear giant cells in certain particular proportions and arrangements. The tumor shows but little collagenous differentiation of its stroma and almost no evidence of ossification. Stromal cells are really the more significant component.

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431. Pearce, T. V., and Collins, D. H.: Cartilaginous Tumor of Shaft of Ulna, *Brit. J. Surg.* 28:432-435 (Jan.) 1941.

432. Carter, R. M., and Heitzman, H.: Chondroma of Bone, *Tr. West. S. A.* (1939) 49:307-322, 1940.

433. Mayer, L.: Chondrosarcoma of Rib: Five Year Cure After Resection, *J. Mt. Sinai Hosp.* 7:467-470 (Jan.-Feb.) 1941.

434. Lichtenstein, L., and Jaffe, H. L.: Giant Cell Tumor of the Bone, *Bull. Hosp. Joint Dis.* 2:95-104 (July) 1941.

On the basis of the stromal cell detail the authors have classified the giant cell tumor into the three grades as follows:

Grade 1: This is the least aggressive. Stromal cells, though abundant, are not compacted and do not exhibit any appreciable atypism. About one half of any representative series of giant cell tumors of bone will be of this grade. The prognosis is relatively favorable, but recurrence may occur.

Grade 2: Cytologically a tumor of this grade manifests a compact cellular stroma showing definite evidences of atypism. It tends strongly toward recurrence and may eventually undergo malignant transformation.

Grade 3: In this grade are represented the small group of tumors which possess a sarcomatous type of stroma, are frankly malignant and metastasize with abundant compacted stromal cells appearing in whorled arrangement and uniformly showing signs of atypism.

The authors discuss further the diagnosis from the standpoint of the roentgen findings and urge an adequate yet conservatively planned biopsy with frozen section studies.

Between the aforementioned authors and Leucutia, Witmer and Belanger<sup>435</sup> there is good ground for profitable discussion. These three authors report 33 cases of giant cell tumor, in 18 of which treatment was by roentgen therapy alone. The 18 patients showed good results, and the authors conclude that roentgen therapy is the treatment of choice in the treatment of all giant cell tumors and of all pathologic growths related to cystic conditions in bone. Adequate biopsies were not sufficiently frequent in this series. Some of these tumors were in the diaphyses of long bones, while others were in the metaphyses but did not involve the epiphyses. The authors apparently are of the opinion that the giant cell tumor is a product of inflammation and repair rather than a true blastoma.

A five year cure of a benign giant cell tumor with irradiation alone is reported by Edieken.<sup>436</sup> The original roentgenogram shows more metaphysial change than epiphysial, and in other elements it is not typical. However, the aspiration biopsy revealed fairly typical characteristics. A total of 2,223 r units was given in two series over a period of four months.

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435. Leucutia, T.; Witmer, E. R., and Belanger, G.: Late Results in Benign Giant Cell Tumors of Bone Obtained by Radiation Therapy, *Radiology* **37**: 1-17 (July) 1941.

436. Edieken, L.: Benign Giant Cell Tumor: Five Year Cure, *Am. J. Roentgenol.* **44**:884-886 (Dec.) 1940.

The surgical treatment of giant cell tumor is discussed by Inclán.<sup>437</sup> His series of tumors is reported to demonstrate various surgical procedures. In treating those giant cell tumors seen early and without previous interference Inclán follows the usual procedure of curettage. When there is recurrence of the tumor and also when the tumor is of the aggressive type, mass resection is urged. In those cases in which the tumor is seen too late or in which as a result of previous interference there is secondary infection or in which there is no doubt regarding the malignancy of the tumor, amputation is the method of choice.

In his thorough and characteristic manner Meyerding<sup>438</sup> discusses the benign and malignant giant cell tumors of bone from the standpoint of the diagnosis and the result of treatment. He recognizes with Lichtenstein and Jaffe<sup>434</sup> that a confusion exists in regard to this group of tumors. He regards part of the confusion as due to the early use of the term "giant cell sarcoma." He recognizes much similarity of tissue in cases of giant cell tumor, osteitis fibrosa cystica and hyperparathyroid osteodystrophy. These tumors are regarded as radiosensitive and possessing a low degree of malignancy. In this paper there is presented an analysis of 124 patients of whom 19 per cent presented signs of malignancy in giant cell tumors. He recognizes that malignant changes may develop in apparently benign tumors and that an accurate diagnosis can hardly be made without careful microscopic study. The treatment recommended is surgical removal when possible. There is demonstrated increasing value in adequate irradiation alone or as an adjunct to surgical procedures postoperatively. The five year survival rate in this series of benign giant cell tumors is 97 per cent. In those giant cell tumors showing malignant tendencies the five year survival rate is 65 per cent. Meyerding properly contends that this survival rate will be higher when the patients are seen early by those surgeons who have had extensive experience in dealing with this particular type of tumor of bone.

An unusual multiple hemangioma of bone, probably congenital in origin, is described by Pierson, Farber and Howard.<sup>439</sup> At the time of writing the patient was 21 years of age; his condition was diagnosed when he was 16 years of age as hyperparathyroidism. The diagnosis was based primarily on the roentgen demonstration of multiple cystic areas in bone, particularly in the skull and the pelvis, but none of these

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437. Inclán, A.: Surgical Treatment of Giant Cell Tumors, *Cir. ortop. y traumatol.*, Havana **8**:63-87 (July-Sept.) 1940.

438. Meyerding, H. W.: Benign and Malignant Giant Cell Tumors of the Bone: Diagnosis and Result of Treatment, *J. A. M. A.* **117**:1849-1855 (Nov. 29) 1941.

439. Pierson, J. W.; Farber, G., and Howard, J. E.: Multiple Hemangiomas of Bone, Probably Congenital, *J. A. M. A.* **116**:2145 (May 10) 1941.

lesions were below the elbows or the knees. An early biopsy of a lesion in the rib was interpreted as indicating osteitis fibrosa cystica. All other laboratory findings, including detailed blood studies, were essentially normal. On a later biopsy of a lesion in the rib, a diagnosis of cavernous hemangioma was made. To the time of writing these lesions were apparently not progressive, and the patient had remained in excellent general health. The writers point out the possibility of this condition existing when the clinical pictures are not definite in cases of hyperparathyroidism, osteitis fibrosa disseminata or xanthomatosis.

*Glomus Tumor.*—The glomus tumor does not belong in the class of hemangioma, although there are vascular elements that relate it to hemangioma to a certain degree. This tumor is of interest from the standpoint of both diagnosis and treatment.

An interesting description of the clinical picture and physiologic characteristics of glomus tumor in the fingers and the toes is written by Couch.<sup>440</sup> Apparently the glomera have to do with heat regulation and bear a close relation to the sympathetic system. Evidently there is a shunt of blood from the arterioles to the venules when the hand is exposed to cold. The pain in the tumor is similar to the intense pain on exposure to cold. The outstanding symptoms are tumor with severe pain, exquisite tenderness, warmth and pinkness with perspiration and a moderate Horner's syndrome.

Another case of glomus tumor in the finger is reported by Rypins,<sup>441</sup> who presents a good description with sketches of the glomus tumor and with roentgenograms which show cleancut destruction of the cortex of the distal phalanx.

Multiple glomus tumors with four in one finger tip are reported by Plewes.<sup>442</sup> These were progressive for several months and showed improvement following excision.

Glomus tumors with intramuscular lipoma were reported by Hoffmann and Ghormley.<sup>443</sup> One patient had an injury to the knee in 1916, followed by menisectomy in 1918 and excision of the scar in 1928 without relief. There was severe pain localized on the medial aspect of the knee.

440. Couch, J. H.: Glomus Tumors: Clinical Picture and Physiology, *Canad. M. A. J.* **44**:356-357 (April) 1941.

441. Rypins, E. L.: Roentgenologic Aspects of Subungual Glomus Tumor, *Am. J. Roentgenol.* **46**:667-672 (Nov.) 1941.

442. Plewes, B.: Multiple Glomus Tumors: Four in One Finger Tip, *Canad. M. A. J.* **44**:364-365 (April) 1941.

443. Hoffmann, H. O. E., and Ghormley, R. K.: Glomus Tumor and Intramuscular Lipoma: Two Cases, *Proc. Staff Meet., Mayo Clin.* **16**:13-16 (Jan. 2) 1941.



On recent exploration the authors found in the synovium a glomus tumor the size of a bean. This was excised, and the patient was completely relieved.

*Primary Malignant Tumors of Bone.*—The outstanding publication in the study of these malignant tumors has been made by Meyerding<sup>444</sup> and Meyerding and Valls.<sup>445</sup> This is an analytic study of 424 primary malignant tumors of bone observed at the Mayo Clinic, Rochester, Minn. In these cases biopsy was made whenever possible, and consideration was given to Broders' method of gradation in the malignancy of these tumors. The various groups of malignant tumors in this statistical study are as follows:

1. Osteogenic sarcoma including chondrosarcoma accounted for 50.9 per cent of the malignant bone tumors. Sixty-seven and six tenths per cent of the patients were male. The average age was 29.3 years, and over 50 per cent were less than 30 years of age. The average duration of symptoms was ten months, and the history of trauma was given in 44 per cent of the cases. These tumors occurred in the femur in 37.7 per cent of the cases. The treatment of choice was operation, this method giving a five year survival rate of 23.4 per cent. There were no five year survivals among the patients treated otherwise.

2. Fibrosarcoma was the tumor in 38 per cent of the cases. In this group 60.5 per cent of the patients were male. Also 60.5 per cent were less than 30 years of age. The femur was most frequently involved in 34.3 per cent of the cases. A history of trauma was obtained in 39.5 per cent of the cases. With amputation there was a five year survival rate of 40 per cent. In the group of patients treated by roentgen therapy there was a five year survival rate of only 16.7 per cent. In those treated by roentgen therapy there was recognized the lower grade of malignancy.

3. Ewing's tumor was the malignant growth of 114 patients, or 27 per cent. Of these 71.9 per cent were male, and 76 per cent were below 30 years of age. The femur was involved in 26.3 per cent and a history of trauma was elicited from 35.1 per cent. The five year survival rate after roentgen therapy alone was 37.5 per cent. After biopsy and roentgen therapy the five year survival rate was 20.5 per cent. After excision of the tumor with or without roentgen radiation, the survival rate was 16.7 per cent. Amputation alone or the combination of amputation with roentgen therapy or with Coley's toxin or with both showed a five year survival rate of 24.2 per cent.

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444. Meyerding, H. W.: Malignant Tumors of Bone, Proc. Staff Meet., Mayo Clin. 16:70-71 (Jan. 29) 1941.

445. Meyerding, H. W., and Valls, J. E.: Primary Malignant Tumors, J. A. M. A. 117:237-243 (July 26) 1941.

4. Multiple myeloma was present in 9.7 per cent of the cases in these series. Of these patients 75.6 per cent were male and 73.2 per cent were between the ages of 40 and 70 years. In 51.2 per cent of the cases there were multiple lesions. A history of trauma was given in 31.7 per cent. Only 1 patient, 3.6 per cent of this series, survived for more than five years.

5. Giant cell sarcoma, or the malignant giant cell sarcoma, was present in 1.6 per cent of the cases in this series; in 83.3 per cent the patients were under the age of 40. For this small group, the five year survival rate was 83.3 per cent.

From such an extensive study it is proper to quote verbatim the author's general impressions:

It is obvious, from long experience, that roentgenologic treatment of tumors of bone is not a cure. Yet, such treatment has an important field of usefulness. Roentgen rays are invaluable in diagnosis, prognosis and treatment of certain types of tumors, especially Ewing tumors, and furnishes the earliest knowledge of the presence of pulmonary metastasis. The possibilities of irradiation, we believe, have not been exhausted, and with the passage of time its application will be improved and its therapeutic value increased.

We are firmly convinced that surgical operation offers the best method of treatment for the majority of primary malignant tumors of bone.

We urge surgeons, roentgenologists and pathologists to cooperate, for only through their combined efforts will diagnosis, prognosis and therapeutic measures be improved. Equally important is education of the practitioner of internal medicine in recognizing the presence of these malignant tumors and in seeking immediate consultation with those experienced and qualified to give advice. Only through early diagnosis, efficient early treatment and careful follow-up investigation can more extremities and lives be saved than have been saved in the past.

*Osteogenic Sarcoma.*—A series of 160 cases of osteogenic sarcoma has been studied by Coley and Pool<sup>446</sup> from the standpoint of prognosis. The prospect of five year survivals is most favorable in patients between the ages of 20 and 40 years; it is least favorable in the first decade or after the fourth decade. Osteogenic sarcoma superimposed on Paget's disease gives an extremely bad prognosis. These conditions are found usually in the fifth, sixth and seventh decades of life. In general the five year survival rate for female patients was found to be 23 per cent; for male patients, 18 per cent. The more peripheral the lesion, the more favorable was found to be the outcome. Grouped according to the various gradations of malignancy, the patients with low grade lesions showed a 40 per cent five year survival rate; those with tumors of intermediate grade malignancy showed a 16 per cent survival rate, and those with

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446. Coley, B. L. and Pool, J. L.: Factors Influencing Prognosis in Osteogenic Sarcoma, *Ann. Surg.* **112**:1114-1128 (Dec.) 1940.

growths of high grade malignancy, a 15 per cent survival rate. Of those patients on whom amputation was done 35 per cent survived five years when the amputation was done through the bone involved; 21 per cent survived when there was disarticulation at the joint above the involved bone, and 36 per cent showed a five year survival rate when amputation was done through the bone proximal to the bone which was affected. Roentgen therapy alone gave only a 9 per cent five year survival rate. Amputation with preoperative conservative surgical procedures or with preoperative roentgen therapy gave a five year survival rate of 32 per cent.

Apparently in this series of osteogenic sarcoma the therapeutic agents used had been narrowed down to roentgen therapy and operation. With the radical surgical attack showing the higher percentage of five year survivals, further elucidation of the time factor between the onset of the disease and the institution of radical operation would be of major interest as an element in prognosis.

In an analysis of 80 cases of osteogenic sarcoma Badgley and Batts<sup>447</sup> show that this is primarily a disease of young and especially of male patients, that trauma occurs in one third of the cases, that the average duration is thirteen months, that pain and swelling are the outstanding findings and that 50 per cent of these tumors occur about the knee region. Their treatment of choice is amputation, and the mortality rate for this series is 79 per cent with an average duration of forty-one months. Their five year survival rate is 19 per cent and their ten year survival rate is 5 per cent. One patient is described as surviving thirteen years after midthigh amputation and dying of pulmonary metastasis. These authors regard the prognosis more favorable for patients over 20 years of age and definitely less favorable for patients with a relatively short duration of signs or symptoms before coming for observation. The prognosis varies with the degree of differentiation of tumor tissue as an index of the grade of malignancy, and the prognosis becomes progressively better as the patient outlives his lesion after its surgical removal. The authors do not feel that biopsy carefully performed will increase the danger of dissemination of the tumor.

Another communication by Batts<sup>448</sup> shows a review of 27 cases of periosteal fibrosarcoma. These were taken from a series of 200 primary malignant growths in bone. The author's analysis shows that 78 per cent of the patients were under 40 years of age and that 63 per cent were

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447. Badgley, C. E., and Batts, M., Jr.: Osteogenic Sarcoma: Analysis of Eighty Cases, *Arch. Surg.* **43**:541-550 (Oct.) 1941.

448. Batts, M., Jr.: Periosteal Fibrosarcoma, *Arch. Surg.* **42**:566-576 (March) 1941.

male. The average duration of symptoms was twenty months, pain being deep seated and swelling being firm and moderately tender. The superficial vessels were not commonly dilated, and the site of the lesions was near the ends of the long bones. The roentgen appearance was that of smooth bone with erosion under the tumor or a reactive thickening and roughening of the cortex. True bone formation was not present. Batts states that these tumors arise from the fibrous layer of periosteum, that they are similar to any other type of fibrosarcoma and that the osseous changes are altogether secondary. Treatment was by roentgen therapy, excision or amputation or a combination of these three methods. Improvement was noted from roentgen therapy, and in some cases the pulmonary metastases were cleared. This is contrary to the usual supposition that fibrosarcoma of bone is usually radioresistant. In this series there was a 40 per cent five year survival rate. Apparently the author feels that the grade of malignancy of the tumor as indicated by microscopic study is the major element in prognosis.

In an exhaustive discussion of roentgen considerations in the diagnosis and the treatment of primary malignant tumors of bone Howes and Schenck<sup>449</sup> report 40 cases and summarize the characteristics of each type of tumor. In their opinion the best treatment is a combination of roentgen therapy and operation. They present a classification which follows essentially the classification of the Committee of the Registry of Bone Sarcoma of the American College of Surgeons. The first three groups include the tumors arising from elements essential in the formation of bone:

I. Osteogenic series—sarcoma

1. Medullary and subperiosteal
2. Telangiectatic
3. Sclerosing
4. Periosteal
5. Fibrosarcoma
  - a. Medullary
  - b. Periosteal
6. Parosteal or capsular

II. Chondroma series

1. Chondrosarcoma
2. Myxosarcoma

III. Giant cell tumor series

1. Malignant

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<sup>449</sup>. Howes, W. E., and Schenck, S. G.: Roentgenologic Considerations in Diagnosis and Treatment of Primary Malignant Bone Tumors, *Radiology* **37**: 18-34 (July) 1941.

## IV. Angioma series

1. Angioendothelioma
2. Diffuse endothelioma or Ewing's tumor

## V. Myeloma series

1. Plasma cell
2. Myelocytoma
3. Erythroblastoma
4. Lymphocytoma

## VI. Reticulum cell sarcoma

1. Lymphosarcoma

## VII. Liposarcoma

Central chondrosarcoma of the femur in a patient 6 years of age is reported by Kennedy.<sup>450</sup> This tumor was resected by curettage, cauterized with 50 per cent solution of zinc chloride and radiated post-operatively. This boy was in good general health with no evidence of local recurrence at the end of six years. The femur shows but 1 inch (2.5 cm.) shortening. This tumor is classified in the Registry of Bone Sarcoma as an osteogenic sarcoma, chondrosarcoma type, and the prognosis is good. In a discussion it is brought out that central chondroma occurs commonly in the bones of the hand, the feet and the spine, also in the ribs and rarely in the long bones. [Ed. NOTE: Geschickter and Copeland report an incidence of only 5 in 2,000 cases. Apparently as a result of its rarity, this tumor is classed simply as chondrosarcoma in order to give it a pigeonhole. In view of the early onset of the tumor in the author's case with no evidence of recurrence after six years there seems to be room for argument as to whether this was simple chondroma or chondrosarcoma of low grade malignancy.]

Turner<sup>451</sup> reports simply the successful hindquarter amputation for chondrosarcoma of the ilium in a patient 49 years old. This man presented generalized osteitis deformans. The case is apparently presented from the standpoint of the technic rather than from the standpoint of the disease itself.

*Myeloma.*—Paul and Pohle<sup>452</sup> review 45 cases of myeloma from the literature and add 4 of their own. In some cases myeloma, solitary for a long period, eventually develops multiple lesions. In this series of

450. Kennedy, R. H.: Central Chondrosarcoma of Femur, *Ann. Surg.* **114**: 1106-1110 (Dec.) 1941.

451. Turner, G. G.: Hind-Quarter Amputation for Chondrosarcoma, *Proc. Roy. Soc. Med.* **34**: 562-563, (July) 1941.

452. Paul, L. W., and Pohle, E. A.: Solitary Myeloma of Bone: Review of Roentgenologic Features, with Report of Four Additional Cases, *Radiology* **35**: 651-666 (Dec.) 1940.

cases, 35 patients were male, and the average age was 48 years. The most frequent locations of the lesion are the spine, the pelvis and the proximal portion of the femur. Bence Jones proteinuria will be present in 20 per cent of the cases but usually only after the lesions become generalized. The roentgen characteristics may be either the osteolytic, very multicystic in appearance similar to the giant cell, or the osteolytic with trabeculations and with less tendency for expansion. In the spine the tumor tends to cross the intervertebral disk, but there is no proliferation of bone. The authors regard these tumors as radiosensitive. Their entire study tends to support the viewpoints that multiple myeloma is the result of metastasis from a primary focus and that there are varying grades of malignancy between the local benign form and the multiple, which may be highly malignant. In their opinion roentgen therapy is the most effective single agent; however, they do urge biopsy with excision of the tumor if this is solitary and surgically accessible. They feel that biopsy followed by roentgen treatment alone seems to offer the best prognosis. In this series 41 tumors were of the plasma cell type.

A questionable solitary myeloma of the spine with involvement of the cord is reported by Kamman.<sup>453</sup> The tumor was extradural; the bone involvement was not gross, but plasma cells were demonstrated in the neural arch. The case report is rather incomplete because there are no roentgenograms of the skull, the pelvis or the long bones.

Another case of plasma cell myeloma of the femur with three pathologic fractures over a period of twelve years and with a coexisting cystic lesion in a rib in which biopsy was not done is reported by Kirsch.<sup>454</sup> [ED. NOTE: For a long period this was clinically regarded as a giant cell tumor.]

Two cases of multiple myeloma are reported. The 1 reported by Perillo<sup>455</sup> represents something of a rarity on account of the early age of the patient, 25 years. There were associated no proteinuria, a normal serum protein, a high blood calcium and persistent hypertension without cardiorenal damage. The second case, reported as a Cabot case,<sup>456</sup> was one of diffuse plasma cell myeloma with elevated serum protein, phosphatase and spinal fluid protein. There was persistent anemia without definite roentgenographic change and no Bence Jones proteinuria. The diagnosis was made by sternal puncture and confirmed at autopsy.

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453. Kamman, G. R.: Solitary (?) Myeloma of Spine with Cord Involvement: Case Report, *Minnesota Med.* **24**:210-212 (March) 1941.

454. Kirsch, I. E.: Plasma-Cell Myeloma of Bone of Over Twelve Years' Duration, *M. Bull. Vet. Admin.* **18**:96-97 (July) 1941.

455. Perillo, J. A.: Multiple Myeloma: Report of Unusual Case, *Radiology* **36**:741-744 (June) 1941.

456. Diffuse Plasma Cell Myeloma, Cabot Case 27131, *New England J. Med.* **224**:559-564 (March 27) 1941.

Grossly allied with myeloma is the solitary plasmocytoma reported by Willis.<sup>457</sup> He regards this solitary plasmocytoma as probably a distinct entity and not merely as an early localized stage of multiple myeloma. He describes a focal tumor destroying the second cervical vertebra. This patient had pain localized in the cervical region for only three months; there was a history of footdrop for a period of twenty years, and the condition had been originally diagnosed as neurosyphilis. However, the Wassermann test gave negative results, and no other lesions were found at autopsy. Willis gives a good review of the literature and feels that only 13 of the reported cases of solitary plasmocytoma may be regarded with certainty. He feels that if the lesions remain solitary for a year the diagnosis is more certain. He feels that these lesions present a good prognosis with adequate operation or adequate roentgen therapy.

The literature on solitary eosinophilic granuloma is reviewed by Bass.<sup>458</sup> The previously reported 8 cases are reviewed, and to these the author adds 2 cases. In 1 of his patients the site of the tumor was the skull, and in the second patient, a rib. These tumors present characteristics suggestive of Hand-Schüller-Christian disease; they are well localized, rapidly growing and markedly osteolytic. One of the author's patients showed extreme eosinophilia of 11.5 per cent. The tissue section shows large cells with pale nuclei and heavy eosinophilic polymorphonuclear infiltration. Bass treated his 2 patients with wide excision and postoperative radiation. He reports no recurrence to the time of writing.

As an interesting side light to the aforementioned study, Bass<sup>459</sup> reports 3 cases of unusual eosinophilia in children. There was associated general adenopathy with marked leukocytosis. Without bony manifestations, these cases were regarded by Bass as probably cases of a chronic infectious condition with the definite diagnosis undetermined.

*Ewing's Tumor.*—There is the still continuing discussion as to the primary nature of Ewing's tumor. Colville and Willis have expressed the views that the primary nature of Ewing's tumor is unproved and that the tumor may be a metastasis from an adrenal neuroblastoma or neurocytoma.

Gharpure<sup>460</sup> reports a case of an untreated Ewing tumor with a complete autopsy. The lesion was primary in the femur. Its recognized

457. Willis, R. A.: Solitary Plasmocytoma of Bone, *J. Path. & Bact.* **53**: 77-85 (July) 1941.

458. Bass, M. H.: Solitary Eosinophilic Granuloma of Bone, *Am. J. Dis. Child.* **61**:1254-1262 (June) 1941.

459. Bass, M. H.: Extreme Eosinophilia and Leukocytosis: Unusual Clinical Syndrome of Unknown Origin Occurring in Childhood, *Am. J. Dis. Child.* **62**:68-79 (July) 1941.

460. Gharpure, V. V.: Endothelial Myeloma (Ewing's Tumor), *Am. J. Path.* **17**:503-508 (July) 1941.

duration was two months. At autopsy there was a solitary pulmonary metastatic nodule. There were no findings which could be regarded as primary neuroblastoma. Gharpure states that the doubt recently expressed concerning the existence of the entity of Ewing's tumor of bone is untenable.

In an article on the histogenesis Foote and Anderson<sup>461</sup> briefly review the literature concerning the origin of Ewing's tumor, the reticuloendothelial primitive mesenchymal cell, the lymphoblasts, the hemocytoblasts, the cells in round cell sarcoma and those of lymphangeal endothelioma.

There is a case reported of a Ewing tumor of a rib in which the histologic picture was dependable because there was no previous therapy. The section of this tissue shows definite vasoformative properties. In their opinion "the thesis of the origin of Ewing's tumor in vascular endothelium is sustained."

In the effort to find data to aid in the gradation of malignancy of Ewing's tumor, Campbell and Hamilton<sup>462</sup> review the clinical records and the tissue sections of 30 patients. They have not followed the usually accepted gradation of malignancy as suggested by Broders on account of the difficulty encountered by the lack of differentiation of the tumor cells. To the authors the most significant findings are the nuclear chromatin content and the cell activity as shown by the mitotic figures. They regard the larger number of chromatin knots as indicative of higher grades of malignancy. They divide the tumors into three grades according to the number of the mitotic figures in each high power field: grade 1: 1 to 5; grade 2: 6 to 10; grade 3: 11 to 15.

Of the patients with tumors of grade 1 malignancy, 31 per cent showed a five year survival rate, and 23 per cent showed a ten year survival rate. Of those with tumors of grade 2 malignancy, 33 per cent showed a survival rate of over five years, but none lived over ten years. For those with tumors of grade 3 malignancy, the prognosis was slightly over one year.

In correlating the cytologic studies with the roentgen findings, the authors feel that the bone condensation accompanies increased cellular activity in the early stages but that the late bone changes are usually accompanied by diminished cellular activity. They regard this series as too small to draw definite conclusions from, but certainly the report is an aid from the standpoint of prognosis.

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461. Foote, F. W., Jr., and Anderson, H. R.: Histogenesis of Ewing's Tumor, *Am. J. Path.* **17**:497-502 (July) 1941.

462. Campbell, W. C., and Hamilton, J. F.: Gradation of Ewing's Tumor (Endothelial Myeloma), *J. Bone & Joint Surg.* **23**:869-876 (Oct.) 1941.



An interesting study by Edwards<sup>463</sup> of a reticulum cell sarcoma, primary in the first lumbar vertebra, is reported together with the autopsy findings. The author describes 17 previously reported cases and adds 1 of his own. These tumors occur mostly in adolescents and young adults. The sites most commonly involved are the femur, the tibia and the clavicle. Roentgen characteristics are not sufficiently clearcut for definite diagnosis. These tumors are regarded as malignant, but the prognosis is relatively good.

*Synovial Sarcoma.*—The most valuable contribution on synovial sarcoma in the literature of the past year is a clinical and pathologic study of this tumor in joints, bursas and tendon sheaths by De Santo, Tennant and Rosahn.<sup>464</sup> Their study includes a brief historical review with a report of 16 cases. They divide synovial sarcoma into three types: encapsulated, circumscribed and diffuse. The encapsulated sarcoma arises most often in the periarticular bursas; the circumscribed tumor is in bursas or tendon sheaths, and the diffuse tumor is found most frequently in the knee. Grossly these tumors are usually soft and myxomatous with focal areas of calcification, chondrification and ossification. About half of the 37 cases reported have occurred in knee joints. Trauma and a preexisting bursitis were frequent factors in causation. The average age of occurrence was 34 years, and most patients were male. There were symptoms of mild pain in 50 per cent; the tumor was evident in over half for an average of twenty-nine months. Dysfunction was common, and swelling occurred in a few cases of intra-articular tumor. The average duration of symptoms was thirty-six months. On roentgen study there is apparent soft tissue tumor with occasional irregular calcification.<sup>465</sup> The usual treatment is excision; this is frequently followed by recurrence of metastasis. Delayed amputation gives the same type of result. The effect of roentgen therapy has not yet been evaluated. De Santo, Tennant and Rosahn recommend: first, widespread excision of the encapsulated tumors with deferring of amputation until the first evidence of recurrence of the tumor; second, the treatment of inaccessible tumors by immediate amputation; third, roentgen therapy, which may retard the growth of some tumors and may be of value after excision of the tumor.

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463. Edwards, J. E.: Primary Reticulum Cell Sarcoma: Case with Autopsy, *Am. J. Path.* **16**:835-844 (Nov.) 1940.

464. De Santo, D. A.; Tennant, R., and Rosahn, P. D.: Synovial Sarcomas in Joints, Bursae, and Tendon Sheaths: Clinical and Pathological Study of Sixteen Cases, *Surg., Gynec. & Obst.* **72**:951-981 (June) 1941.

465. Aitken, A. P.: Roentgenographic Recognition of Synovioma, *J. Bone & Joint Surg.* **23**:950-952 (Oct.) 1941.

In discussing the tumor from the histologic point of view, the authors state that the synovial cells are related to the reticuloendothelial system and are capable of three functions, viz., formation of endothelial lining, mucin and histiocytes. Multiple sections of the tumors are necessary because the tumor may be heterogenous, may have epithelioid glandlike spaces, may be pavement-like with mucin production or may be grossly myxomatous. The histiocytic type resembles the reticulum cell sarcoma and the polymorphous sarcoma with sheets of xanthomatous cells. Any fibrosarcoma or spindle cell sarcoma in or near a joint is likely to be synovial sarcoma; the proof depends on painstaking pathologic investigation. The least malignant of these tumors show a high degree of histiocytic differentiation, while the most malignant are probably those with closely packed round oval cells with abundant reticulum.

A similar report of 4 cases of synovial sarcoma is made by Jaffe and Lichtenstein.<sup>466</sup>

Herzmark<sup>467</sup> reports a giant cell synovial tumor of the knee treated by excision. This was followed in six months by recurrence: after roentgen therapy there was no more trouble for at least one year. [ED. NOTE: This was probably a synovioma, although no mention of mitosis is made in the pathologic report.]

Hutchison and Kling<sup>468</sup> present a case report of malignant synovioma in the knee treated by excision and roentgen therapy. The patient died at the end of seven years. This tumor was of the solid type and consisted mostly of spindle cells.

Leichner and Schaefer<sup>469</sup> report a case of synovial sarcoma arising from the gluteal bursa in a 10 year old girl. They state that radical amputation is essential and that roentgen therapy is of no value.

Herson<sup>470</sup> reports a benign synovioma arising in one of the bursas about a knee. This followed trauma. On histologic study this tumor was benign, and fifteen months after excision there had been no recurrence.

The roentgen recognition of synovioma is discussed by Aitken,<sup>465</sup> who states that a provisional diagnosis of synovioma can be made when

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466. Jaffe, H. L., and Lichtenstein, L.: Sarcoma (Synovioma), *Bull. Hosp. Joint Dis.* **2**:3-10 (Jan.) 1941.

467. Herzmark, M. H.: Giant Cell Synovial Tumor of Knee, *J. Bone & Joint Surg.* **23**:684-686, (July) 1941.

468. Hutchison, C. W., and Kling, D. H.: Malignant Synovioma, *Am. J. Cancer* **40**:78-84 (Sept.) 1940.

469. Leichner, W., and Schaefer, A.: Synovial Sarcoma: Case Report, *Connecticut M. J.* **5**:113-115 (Feb.) 1941.

470. Herson, R. N.: Benign Synovioma Arising in Bursa, *Brit. M. J.* **1**:52 (Jan. 11) 1941.

the tumor mass is rounded, lobulated and sharply defined and contains scattered or irregular deposits of amorphous lime. He presents a case report in which the patient was a 21 year old man with a definite history of trauma two years preceding the development of the tumor.

A giant cell xanthoma is reported by Conzett and Young.<sup>471</sup> Their patient was a 63 year old white man in whom after trauma to the wrist a mass developed on the dorsum. This mass had been present for five years. The tumor surrounded the tendons of the extensor of the thumb and the index finger. The histologic diagnosis was giant cell xanthoma of the tendon sheath, and there had been no recurrence nine months after excision.

*Metastatic New Growths in Bone.*—The clinical syndrome and the early diagnosis of metastatic carcinomatous lesions of the spine are well portrayed by Wolfson, Reznick and Gunther.<sup>472</sup> They believe that early diagnosis can be made before changes in the bone are evident on roentgen examination. They state that at least 1 sq. cm. of the vertebral body must be destroyed before the changes are apparent in a roentgenogram. They stress pain as the earliest symptom. It is the characteristic root pain limited to a definite dermatome aggravated by sudden jarring, sneezing or bending. The zone is narrower in cases of arthritis. It is constant as contrasted with the intermittent pain of arthritis or myositis and neuralgia. In cases of arthritis motion does give some relief at times. This is not true of the pain due to metastatic carcinoma. The percussion tenderness over the spine is constant. The authors insist that there is persistent elevation of the sedimentation rate in those cases in which there are bone metastases; they state also that the phosphatase level is high with the osteoblastic lesions and high or normal with the osteoclastic lesions. In their experience early roentgen therapy affords relief; hence early diagnosis of metastasis is important.

In considering the differential diagnosis of carcinoma of the prostate with skeletal metastasis and osteitis deformans, deVries<sup>473</sup> writes particularly from the urologic viewpoint. It is his opinion that a digital prostatic examination suffices to make a diagnosis of carcinoma of the prostate in 90 per cent of the cases of this type. In the remaining cases

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471. Conzett, D. C., and Young, E. R.: Giant Cell Xanthoma of Wrist, J. Iowa M. Soc. **31**:29-31 (Jan.) 1941.

472. Wolfson, S. A.; Reznick, S., and Gunther, L.: Early Diagnosis of Malignant Metastases to Spine: Clinical Syndrome, J. A. M. A. **116**:1044-1048 (March 15) 1941.

473. deVries, J. K.: Differential Diagnosis of Carcinoma of Prostate with Skeletal Metastases and Osteitis Deformans (Paget's Disease of Bone), J. Urol. **46**:981-996 (Nov.) 1941.

cystoscopy, cystourethrography and biopsy may be necessary to confirm the diagnosis. He demonstrates well the punch aspiration biopsy as a diagnostic procedure.

Adenocarcinoma of the male breast of the scirrhus type with generalized bone metastasis is reported by Livingston.<sup>474</sup> The patient had extremely widespread osteolytic metastasis. [ED. NOTE: Geschickter and Copeland report only 1 case of metastatic lesion in a male patient in 100 cases of cancer of the breast.]

A rare leukemoid reaction in a case of carcinomatous skeletal and splenic metastasis from bronchiogenic carcinoma is reported by Lisa, Solomon and Gordon.<sup>475</sup> There are extremely few cases of metastatic carcinoma reported in which immature myeloid cells are noted frequently in the circulating blood. In this case of bronchiogenic carcinoma with metastasis there were leukemoid reaction, purpura and relative and absolute lymphocytosis. The tumor and the metastases were anaplastic with cords of cells and diffuse invasion without real tumor formation. [ED. NOTE: These cases are of interest so far as the blood picture may confuse the diagnosis.]

Squamous cell carcinoma arising in a chronic osteomyelitic sinus tract and developing metastatic lesions is shown in 2 cases by Bereston and Ney.<sup>476</sup> They have reviewed the literature well and added these 2 new cases. Malignant degeneration in chronic osteomyelitis from sinus tracts occurs in men 40 to 60 years of age with a history of osteomyelitis from a sinus tract of twenty to thirty years' duration. The bones most commonly affected are the tibia, the femur and the bones of the hand. The local signs are a cauliflower mass or a foul discharge from the deep sinuses. The lesions are proved by biopsy and roentgen examination. Metastasis from this type of carcinoma is rare, only 7 cases having been previously reported. Of the 2 cases added, in one there was metastasis to the lung, in the other, to the pelvis. The rarity of metastasis in this type of lesion is explained by the low grade of malignancy or by the possibility that some of the cases of carcinoma reported may have been instances of pseudoepitheliomatous hyperplasia rather than of true malignant tumor.

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474. Livingston, S. K.: Adenocarcinoma, Scirrhus Type of Left Male Breast with Generalized Bone Metastasis: Case Report, *Am. J. Roentgenol.* **45**:589-590 (April) 1941.

475. Lisa, J. R.; Solomon, C., and Gordon, E. J.: Leukemoid Reaction in Carcinomatous Skeletal and Splenic Metastases: Case Report, *Am. J. Cancer* **40**:227-230 (Oct.) 1940.

476. Bereston, E. S., and Ney, C.: Squamous Cell Carcinoma Arising in Chronic Osteomyelitic Sinus Tract with Metastasis, *Arch. Surg.* **43**:257-268 (Aug.) 1941.

In the literature on malignant tumors of the parathyroid gland as reviewed by Gentile and associates,<sup>477</sup> 21 cases have been reported. These authors report a case of malignant disease of the parathyroid with local metastasis and multiple pathologic fractures. Five years after removal of the parathyroid tumor the patient was alive and well. The fractures were well healed, and there was moderate recalcification of bone.

The roentgen manifestations of skeletal metastasis from neuroblastoma are presented by Ackermann<sup>478</sup> in his report of 4 cases. This is a fairly complete discussion of a rare entity. The embryologic development of the sympathetic nervous system is shown to be of the same origin as that of the medulla of the adrenal gland. Neuroblastomas arise from sympathetic neuroblasts, which are undifferentiated migratory cells. These arise in the adrenal medulla or the adjacent sympathetic ganglions. Neuroblastoma occurs in children, usually while they are under 3 years of age. According to the distribution of metastasis there are two types. In one type metastasis is found in viscera and later in the flat bones. In the other type there is metastasis to the skull first; there is local swelling, proptosis, discoloration of the eyelid and profound secondary anemia. The course is rapidly fatal. The roentgen appearance is that of an osteolytic tumor with periosteal reaction similar to Ewing's tumor or osteogenic sarcoma. The differential diagnosis with regard to syphilis or chloroma may be extremely difficult.

A review of the literature on subungual melanoma is made by Scannell<sup>479</sup> in connection with the report of a single case. He states that the incidence is 1 in 18,752 new hospital admissions. It is uncommon in Negroes. It occurs more frequently in older people. There is a history of trauma in more than one half of the cases. The lesion begins as a paronychia and often develops as a black fungating ulcer elevating the nail. There is a pathognomonic coal black border along the edge of the nail involved. The dressings are often stained brown. The growth is usually slow, spreading to the inguinal and axillary nodes first. Then it may go to wide metastasis. On microscopic examination there are two types of cells, the spindle and the polygonal with alveolar arrangement. The tissue is friable, and frozen sections are difficult. The author advises amputation with resection of the regional glands as the treatment of

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477. Gentile, R. J.; Skinner, H. L., and Ashburn, L. L.: Malignant Tumor with Osteitis Fibrosa Cystica: Parathyroid Glands, *Surgery* **10**:793-810 (Nov.) 1941.

478. Ackermann, A. J.: Neuroblastoma, with Special Reference to Roentgen Manifestations, *J. Oklahoma M. A.* **34**:241-246 (June) 1941.

479. Scannell, R. C.: Subungual Melanoma: Report of Case, *Am. J. Surg.* **53**:163-167 (July) 1941.

choice. These tumors are radioresistant. Five year survival rate is about 25 per cent.

An amelanotic melanoma is reported<sup>480</sup> which is regarded as a non-pigmented mole. The ulcerating mass was removed from the toe in 1923. In 1938 the patient returned with metastasis in the femoral nodes. These metastases became widespread to the skin, the tonsils, the heart, the mediastinum, the omentum and the adrenals. This case is confusing from its beginning.

*New Growth Superimposed on Previously Existing Pathologic Growth.*—Bennett and Berkheimer<sup>481</sup> report on malignant degeneration of multiple benign exostosis in a boy with anaplastic changes in a benign osteoma of the lower end of the femur. They present a genetic history showing many benign exostoses in the family but no definite mendelian pattern and no cases of malignant exostosis. In a nephew of this patient a comparable benign tumor was demonstrable at the age of 5 months. The authors in their discussion show a distinct relation of this group of tumors to chondroma or enchondroma. From their review of the literature it is apparent that malignant change in multiple benign exostosis is relatively rare. The type of malignant growth encountered is usually osteogenic sarcoma, but the grade of malignancy is distinctly less than that of the malignant growth of the primary type. The treatment of choice is amputation, but high voltage roentgen therapy is of value if amputation is not permissible.

There are two interesting articles on osteosarcoma with extraskeletal bone formation bearing a close resemblance to osteogenic sarcoma. Mayer and Friedman<sup>482</sup> report a painful swelling in the calf of the leg of a 17 year old girl, existing for five weeks and growing rapidly with no history of trauma. From the site of the tumor there was removed a large sheet of fascia, thick, firm in consistency and having a central marble-like mass of bone. The tissue was studied by four pathologists, each reporting an osteogenic sarcoma. Amputation was done through the lower third of the thigh, and for eight years there was no evidence of recurrence. In view of the benign course of the disease the authors doubt the diagnosis of osteogenic sarcoma and call attention to the close

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480. Amelanotic Melanoma: Case Report, Connecticut M. J. 5:193-196 (March) 1941.

481. Bennett, G. E., and Berkheimer, G. A.: Malignant Degeneration in Case of Multiple Benign Exostoses with Brief Review of Literature, Surgery 10:781-792 (Nov.) 1941.

482. Mayer, L., and Friedman, M.: Extra-Skeletal Bone Forming Tumor of Fascia, Resembling Osteogenic Sarcoma, Bull. Hosp. Joint Dis. 2:187-192 (Oct.) 1941.

resemblance of this tissue to the metaplastic benign tumors described by Mallory. Two others were described by Geschickter and Maseritz. Mayer and Friedman state:

The lesion is an atypical form of myositis ossificans and arises apparently from a young fibroblast, which by the process of metaplasia, differentiates into various types of connective tissue elements, including osteoid tissue and bone. . . . The absence of atypism, tumor giant cells, or a significant number of mitotic division figures rules out an osteogenic sarcoma.

Wilson<sup>483</sup> reports 10 cases of extraskeletal ossifying tumors or osteosarcoma. In this group there were 4 osteogenic sarcomas, 1 fibrosarcoma, 1 chondrosarcoma, 1 bursal sarcoma with ossification, 1 case of von Recklinghausen's disease with ossification in a neurofibroma and 2 fibrous osteomas. The author feels that the potency of neoplastic mesoblastic tissue goes in almost any direction; also, that myositis ossificans offers the most difficulty in distinguishing heteroplastic from neoplastic bone formation.

A fibrosarcoma developing in the scar of an old burn is described by Fleming and Rezek.<sup>484</sup> The scar had existed for forty-nine years. Wide excision of the tumor with a skin graft covering the defect was done. Regional gland metastasis developed, and the patient died nineteen months after the operation. Autopsy showed visceral metastasis as well. These authors state that there have been 2 other sarcomas which developed in the skin after trauma.

Zieman<sup>485</sup> reports a tumor on the tip of a finger within a few months after trauma. Four years after this trauma the tumor was resected and showed microscopically "a fibrogenic fibrocellular sarcoma."

In this group of cases could well be included an ossifying fibroma of the thenar space reported by Kyle.<sup>486</sup> The pathologic growth reported was that of an ossifying fibroma; more detailed history was not given.

A case of meningeal tumor with both osteoblastic and osteoclastic activity was related by Turner and Craig.<sup>487</sup> This is a single case report, but it is accompanied by a good discussion of bone formation and soft

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483. Wilson, H.: Extraskeletal Ossifying Tumors, *Ann. Surg.* **113**:95-112 (Jan.) 1941.

484. Fleming, R. M., and Rezek, P. R.: Sarcoma Developing in Old Burn Scar, *Am. J. Surg.* **54**:457-465 (Nov.) 1941.

485. Zieman, S. A.: Fibrosarcoma of Soft Parts of Extremities, *Surgery* **9**:675-678 (May) 1941.

486. Kyle, B. H.: Ossifying Fibroma in Thenar Space: Case, *Virginia M. Monthly* **68**:165 (March) 1941.

487. Turner, O. A., and Craig, W. M.: Osteogenic Sarcoma of Meningeal Origin: Case of Meningeal Tumor with Both Osteoblastic and Osteoclastic Activity, *Arch. Path.* **32**:103-111 (July) 1941.

tissues. The authors feel that in this case there was sarcomatous transformation of the fibroblastic connective tissue of the tumor. They regard this as rather rare, because most of these processes ordinarily show heteroplastic formation of bone.

In reporting a case in which autopsy was done, Curphey<sup>488</sup> describes diffuse pagetoid osteitis complicated by an osteogenic sarcoma in a patient with syphilis. There were definite syphilitic changes in all organs. Paget's osteitis was atypical with sarcomatous and presarcomatous osteoid tissue in the intratrabecular spaces. The author's diagnosis is pagetiform syphilis of bone with secondary sarcomatous changes. In his review of the literature on Paget's disease in persons with syphilis, he states that all lack histologic proof that the bone changes are not typical of osteitis deformans.

*Tumors of the Spinal Cord.*—In reporting a case of dermoid tumor extending from the second lumbar to the second sacral segment in a boy of 9 years, Bagley and Arnold<sup>489</sup> have selected from the literature 44 cases of intraspinal dermoid and 13 of teratoma. They discuss the unusual symptoms of cauda equina tumor and stress the observation that spasm of the erector spinae and hamstring muscles are suggestive of early signs of cauda equina tumor.

Another rare but interesting entity is a case of von Recklinghausen's neurofibromatosis with an hourglass tumor of the cervical spine reported by Jelsma.<sup>490</sup> This tumor was dumbbell in form with a portion intraspinal and a portion extraspinal and with a connecting portion through the intervertebral foramen or interlaminar space. There are eight references to the literature representing the reports of 89 cases. These tumors occur most commonly in the thoracic portion of the spine, only 22 having been reported in the cervical portion of the spine. They are usually benign, originating from meninges, a nerve root or rarely a ganglion. Intraspinal portions are small, about the size of a hazelnut. The extraspinal portions are the size of a plum or an orange. Eighty per cent of these tumors are visible or palpable in the anterior or the posterior triangle of the neck. The origin and the development of this

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488. Curphey, T. J.: Report of a Case of Diffuse "Pagetoid" Osteitis in a Syphilitic Complicated by Osteogenic Sarcoma, *Urol. & Cutan. Rev.* **45**:438-443 (July) 1941.

489. Bagley, C., Jr., and Arnold, J. G., Jr.: Unusual Symptomatology of Cauda Equina Tumors: Report of Case of Dermoid with Review of Literature of Dermoid and Teratomatous Tumors of Vertebral Canal, *Tr. Am. Neurol. A.* **66**:171-175, 1940.

490. Jelsma, F.: Hour-Glass Tumors of Cervical Spine, *Am. J. Surg.* **52**: 483-488 (June) 1941.



tumor are uncertain. The symptoms are those of spinal cord compression, and roentgenograms often show an enlargement of the intervertebral foramen.

*Surgical Treatment.*—During the past few years there has been a growing tendency toward conservative operation in the treatment of benign tumors of bone and of those malignant tumors of bone of low malignancy and so situated that excision of the tumor can be done with immediate or early replacement by bone grafts. Coley <sup>491</sup> reports 8 cases together with the roentgen findings. In his opinion the growths suitable for conservative operation are the bone cysts, the giant cell tumor, the central chondroma (in spite of its tendency to recurrence) and a few osteogenic sarcomas of low grade malignancy.

Phemister <sup>492</sup> recommends the use of the bone graft in cases of giant cell tumors, in rare cases of early well localized sarcoma and in cases in which amputation is refused. He feels there is a definite place for this type of operation in the treatment of malignant tumors of bone which are centrally located and are of low malignancy and of which an early diagnosis is made.

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491. Coley, B. L.: Conservative Surgery in Tumor of Bone, *South. Surgeon* **10**:379-392, (June) 1941.

492. Phemister, D. B.: Use of Bone Graft in Treatment of Bone Tumors, *Proc. Interst. Postgrad. M. A. North America* (1939), 1940, pp. 24-27.

(To Be Continued)

## EXPERIMENTAL FREEZING SHOCK

### CHANGES IN BODY FLUIDS AND TISSUES

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The thermal injury due to freezing causes the loss of large amount of protein-containing fluid at the site of thawing tissues; this was demonstrated by Harkins and associates.<sup>1</sup> This fluid is derived from the circulating blood plasma, and its loss is accompanied by the development of shock. Mahoney<sup>2</sup> has demonstrated that a similar type of shock results from cooling of peritoneal surfaces. In these respects thermal injuries due to freezing and burns resemble each other closely. In a recent book the clinical applications of these observations have been reemphasized by Harkins.<sup>3</sup> Sir Thomas Lewis<sup>4</sup> described the damage to capillaries, the development of edema and other changes following frostbite.

This study was aided by a grant from Abbott Laboratories, North Chicago, Ill. From the William Buchanan Blood, Plasma and Serum Center, Baylor University Hospital, and the Department of Pathology, Baylor University College of Medicine.

1. Harkins, H. N.: Shock Due to Freezing: I. Shift of Body Fluids and Associated Blood Concentration Changes, *Proc. Soc. Exper. Biol. & Med.* **32**:432-434 (Dec.) 1934. Harkins, H. N., and Hudson, J. E.: Shock Due to Freezing: II. Composition of Edema Fluid, *ibid.* **32**:434-435 (Dec.) 1934. Harkins, H. N., and Harmon, P. H.: Experimental Freezing: Bleeding Volume, General and Local Temperature Changes, *ibid.* **32**:1142-1143 (April) 1935.

2. Mahoney, E. B.: A Study of Experimental and Clinical Shock with Special Reference to Its Treatment by the Intravenous Injection of Preserved Plasma, *Ann. Surg.* **108**:178-193 (Aug.) 1938.

3. Harkins, H. N.: *The Treatment of Burns*, Springfield, Ill., Charles C. Thomas, Publisher, 1942.

4. Lewis, T.: Observations on Some Normal and Injurious Effects of Cold upon the Skin and Underlying Tissues: III. Frost-Bite, *Brit. M. J.* **2**:869-871 (Dec. 20) 1941.

In attempting to produce a pronounced diminution in the blood volume of experimental animals due solely to the loss of plasma from the vascular system, we have found that a modification of Harkins' freezing technic is reliable, consistent in results and simple to perform. Uniform events leading to fatal shock may be expected in each animal after one hindlimb has been severely frozen. This course usually extends over a period of six to ten hours. The effects of the depletion of plasma volume on the tissues both early and late in the experimental period can be observed by arresting the experiment at different intervals. Additional interest in this form of injury results from the probable occurrence of a similar type of shock clinically on modern battlefields, such as the present Russian front.

The method of production of the freezing injury, the apparent shifts of body fluid and the early and late pathologic changes in the various organs, observed grossly and microscopically, are reported at the present time. The effects of therapy with various solutions of serum protein on these and on other animals will be presented later.<sup>5</sup>

### METHODS

Harkins' technic of producing freezing shock, which consists of the application of solid carbon dioxide to one half of the body surface, has been modified in the following manner: The freezing injury was produced by submerging one hindlimb of a medium-sized dog in a freezing solution composed of solid carbon dioxide and 95 per cent alcohol. Approximately 8 pounds (3.6 Kg.) of crushed solid carbon dioxide was placed in a galvanized bucket with a capacity of 2 gallons (7.5 liters). To this 4 to 6 quarts (3.8 to 5.7 liters) of 95 per cent alcohol was added with constant stirring. In ten to fifteen minutes the alcohol became syrupy and reached a temperature well below  $-40^{\circ}\text{F}.$ <sup>6</sup> A half-moon niche along the upper edge of the bucket facilitated the placing of the hindlimb in the freezing mixture. With proper care foaming of the mixture was kept at a minimum. Most of the alcohol was reclaimed later for use in further experiments by filtering it after it had reassumed room temperature.

Medium-sized dogs were subjected to anesthesia induced by slow intravenous injection of 1 grain (0.06 Gm.) of soluble pentobarbital U. S. P. (pentobarbital sodium) for every 5 pounds (2.3 Kg.) of body weight. While the lumps of solid carbon dioxide were agitated with a stirring rod, one hindlimb of the animal was placed in the solution for twenty-five minutes. By placing an asbestos pad against the abdomen an attempt was made to prevent freezing of the abdominal wall. With this protection the freezing extended only slightly above the inguinal ligament. After twenty-five minutes the limb was frozen solid and the freeze extended to the bones (femur and tibia). The dog was then placed on the board,

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5. Muirhead, E. E.; Ashworth, C. T.; Kregel, L. A., and Hill, J. M.: The Therapy of Shock in Experimental Animals with Plasma Protein Solutions: II. Fluid Distribution in the Body and Its Relation to Treatment with Concentrated and Dilute Serum Solutions and Saline Solutions, unpublished data.

6. The resistance thermometer used for measuring the temperature of the mixture read temperatures to  $-40^{\circ}\text{F}.$  only.

and the frozen limb was allowed to thaw at room temperature. The thawing was fairly complete in one to one and one-half hours. As the thawing proceeded the plasma volume decreased. The blood pressure was usually sustained slightly below the control level until fairly late, i. e. five to six hours. Then it dropped either gradually or fairly rapidly, and the animal died approximately eight to twelve hours after the freeze. After its death the extremities were weighed according to the Blalock technic.<sup>7</sup>

In the present experiments the mean arterial pressure was taken by means of a carotid cannula and a mercury manometer. Samples of blood were taken from the femoral and jugular veins, and heparin was used as anticoagulant. The following values were determined before and during shock: hemoglobin concentration of the blood,<sup>8</sup> hematocrit reading,<sup>9</sup> red blood cell count,<sup>10</sup> plasma protein concentration,<sup>11</sup> plasma volume,<sup>12</sup> total circulating proteins, water available for the solution of sodium thiocyanate,<sup>13</sup> plasma sodium concentration<sup>14</sup> and carbon dioxide-combining power of the plasma.<sup>15</sup> The samples of plasma taken during shock invariably were stained with hemoglobin, which indicated that hemolysis had occurred. The possible causes for the hemolysis are discussed hereinafter.

Postmortem examinations of the animals were performed. Tissue was obtained for microscopic examination from the lungs, myocardium, liver, ileum, stomach, spleen, kidneys and adrenal glands and from the muscles and subcutaneous tissues of the frozen limb for microscopic examination. The tissues were stained by the usual hematoxylin-eosin technic.

## RESULTS

The blood pressure was usually depressed for a few minutes immediately following the freeze but soon returned to a level slightly below the control level. Rarely, it was transiently elevated above the control level for a short interval. It remained near the control level for five to

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7. Blalock, A.: Experimental Shock: A Cause of Low Blood Pressure Produced by Muscle Injury, *Arch. Surg.* **20**:959-996 (June) 1930.

8. Sanford, A. H., and Sheard, C.: The Determination of Hemoglobin with the Photoelectrometer, *J. Lab. & Clin. Med.* **15**:483-489 (Jan.) 1930.

9. Wintrobe, M. M.: A Simple and Accurate Hematocrit, *J. Lab. & Clin. Med.* **15**:287-289 (Dec.) 1929.

10. The red cells in twenty hemocytometer squares were counted on each occasion. The red cell counts are not reported in the table but will be presented later.<sup>5</sup>

11. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, *J. Biol. Chem.* **82**:545-550 (May) 1929.

12. Gregerson, M. D.; Gibson, J. J., and Stead, E. A.: Volume Determination with Dyes, *Am. J. Physiol.* **113**:54 (Sept.) 1935.

13. Crandall, L. A., and Anderson, M. X.: Estimation of the State of Hydration of the Body or the Amount of Water Available for the Solution of Sodium Thiocyanate, *Am. J. Digest. Dis. & Nutrition* **1**:126-131 (April) 1934.

14. Butler, A. M., and Tuthill, E.: An application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, *J. Biol. Chem.* **93**: 171-180 (Sept.) 1931.

15. Exton, W. G.; Schattner, F., and Rose, A. R.: Acidosis and Alkalosis: Clinical Significance and Measurement by Colorimetry of Plasma CO<sub>2</sub> Capacity, *Am. J. Clin. Path.* **11**:632-642 (Aug.) 1941.

eight hours, after which it usually dropped gradually to a severe shock level. This late drop was always indicative of impending death. Occasionally, the final drop was sudden with a rapid termination. Hemoconcentration could be observed as soon as thawing began, frequently within a few minutes, and was progressive for an average of five to six hours, after which it remained at a fairly stabilized peak until death. With the hemoconcentration there was a corresponding severe depletion of plasma volume and of total circulating proteins. The concentration of plasma protein was slightly modified by the free hemoglobin present (usually 0.1 to 0.3 Gm. per hundred cubic centimeters) but was not

TABLE 1.—*Blood Pressure and Body Fluid Changes in Six Dogs Before and During Shock\**

Dog	Weight, Kg.	Period	Interval for Development of Late Shock, Hr.	Blood Pressure, Mm. of Mercury	Hemoglobin, Gm. per 100 Cc.	Hematocrit Reading, per Cent	Plasma Volume, Cc.	Plasma Protein, Gm. per 100 Cc.	Total Circulating Proteins, Gm.	Extracellular Water, Cc.	Interstitial Water, Cc.	Plasma Sodium, Mgr. per 100 Cc.	Plasma Carbon Dioxide-Combining Power, Vols. per Cent
7S	9.3	Control		165	15.50	47.0	485	6.10	29.6	3,470	2,965	340	52.6
		Shock	4.5	65	20.10	67.0	265	5.50	14.5	3,280	3,015	346	45.5
12S	8.5	Control		150	15.10	51.5	400	6.20	24.8	2,450	2,050	352	55.5
		Shock	9.5	60	21.00	78.0	265	6.50	17.2	1,520	1,255	374	37.0
13S	10.0	Control		160	12.35	38.5	470	6.10	28.6	1,930	1,460	314	52.0
		Shock	6.5	50	21.15	71.0	210	6.15	12.8	1,340	1,130	355	37.0
15S	7.5	Control		160	15.00	47.0	354	....	....	1,850	1,496	323	63.0
		Shock	7.5	50	21.15	74.0	145	....	....	1,540	1,395	364	41.5
18S	9.1	Control		160	12.80	40.4	525	6.43	33.8	4,040	3,515	376	53.4
		Shock	6.0	55	20.15	60.0	208	5.90	16.7	2,650	2,442	506	25.3
19S	8.5	Control		130	13.25	38.5	470	6.55	30.5	.....	.....	365	45.5
		Shock	7.5	54	19.15	60.0	278	6.70	18.6	.....	.....	415	21.3
Average	8.8	Control		154	14.00	43.6	450	6.27	29.4	2,748	2,301	345	54.5
		Shock	6.9	56	20.45	66.6	229	6.15	15.9	2,066	1,847	393	34.6

\* The weights of the extremities were modified by the treatment and are not recorded here.

consistently changed in any one direction. The water available for the solution of sodium thiocyanate (considered as extracellular water) was consistently decreased. The plasma sodium concentration was increased. These two separate findings are taken to indicate a decrease in extracellular fluid volume. The apparent decrease in extracellular fluid plus an increase in the sodium ion concentration suggests that fluid enters body cells in the late phases of this type of shock. The carbon dioxide-combining power was greatly depressed. The edema fluid of the frozen leg contained an average of 4.0 Gm. of proteins per hundred cubic centimeters. When allowed to stand in a test tube, this fluid clotted.

Fifty dogs have been subjected to this type of shock, 29 of which constitute the basis of this study. The changes in blood pressure and in the body fluids in 6 dogs during shock are presented in table 1. The

effects of therapy with dilute and concentrated solutions of serum and solutions of sodium chloride during the late phase of this shock in 19 dogs will be discussed in a separate report.<sup>5</sup>

#### PATHOLOGIC CHANGES

The tissues of the various organs of different animals were observed at various intervals during the course of the experiments. The pathologic changes in the various organs will be described under two separate heads: First, the changes in the interval up to two and one-half hours after the freeze was completed are described as early observations. Second, the changes noted of the organs when death occurred four or more hours after the freeze are considered under late observations.

*Early Observations.*—Gross Examination: The lungs were pink, were air containing throughout and had dry cut surfaces. The blood that dripped from the cut vessels was usually thick and dark. The pleural spaces and the pericardial sac had no excess of fluid. The myocardium was usually flabby, and the chambers contained a small amount of blood.

The intestines were contracted and pale. The intestinal mucosa was pale. There was no excess fluid in the peritoneal cavity. The cut surface of the liver was brown and oozed thick and dark blood from the larger vessels. The spleen was partly or completely contracted and usually weighed about 20 Gm. Gross changes in the adrenal glands were not discernible.

The appearance of the frozen leg depended on whether thawing had been complete or not. Immediately after the freeze and for a time up to fifteen to forty-five minutes after, the frozen tissues could be seen to extend down to the bones of the limb. The tissues were firm and fairly pale. As thawing proceeded, the skin, the subcutaneous tissue and the muscles became extremely edematous. When a blue dye had been given intravenously, the edema fluid subsequently stained blue. The small vessels and the capillaries were everywhere prominent and dilated. The femoral artery occasionally contained a thrombus, but the vein was usually not obstructed. The skin and the subcutaneous tissue of the other limbs were pale and did not appear edematous.

*Microscopic Examination:* In general, the microscopic changes in shock are vascular, interstitial and cellular. The vascular manifestations are dilatation of venules and capillaries. The interstitial changes consist of edema, infiltration by polymorphonuclear neutrophilic leukocytes and capillary hemorrhages. The cellular changes as considered are confined to parenchymatous organs, such as the liver, the kidneys and the adrenal glands. They are characterized by pyknosis and karyolysis; droplet degeneration of the cytoplasm; acute parenchymatous degeneration, and focal necrosis, atrophy and necrobiosis. These changes have been classified as slight, moderate and marked.

The studies in the period up to two and a half hours revealed slight or no vascular changes and usually no cellular changes in the viscera. The absence or meagerness of the changes was particularly evident in the period up to the first hour. The vascular manifestations in the lungs when present were venular dilatation and extremely slight capillary hyperemia. In the liver venosinusoidal hyperemia was slight or moderate and focal. The kidneys were more prone to display patchy hyperemia. This focal dilatation of capillaries was observed particularly in glomeruli which had only a portion of their capillary loops open and in the peritubular capillaries. The gastric and the intestinal mucosa were normal in appearance. Edema in the frozen leg was proportionate to the state of thawing.

The adrenal glands require special mention. Hyperemia was slight or absent in the cortex and the medulla. The zona fasciculata of the cortex invariably revealed infiltration with polymorphonuclear neutrophilic leukocytes. On one occasion this infiltration was prominent thirteen minutes after the freeze. The parenchymatous cells in this layer appeared well preserved but exhibited a slight decrease in lipid content.

In the 29 carefully studied dogs the interval between the inception of the anesthesia induced with soluble pentobarbital and the beginning of the freeze averaged one hour and twenty-nine minutes. The same period for the 6 dogs studied in the early period following the freeze averaged one hour and twenty minutes. The highest time of this interval for any one dog was two hours and twenty minutes. The adrenal glands from 5 normal dogs killed by a fatal hemorrhage during ether anesthesia were examined microscopically; these animals were considered the basic "anesthesia controls." Four other dogs were subjected to and killed under anesthesia induced with intravenous soluble pentobarbital, and their adrenal glands were studied microscopically; these animals also were used as anesthesia controls. Two of the latter dogs were killed by rapid intravenous injection of additional soluble pentobarbital (5 to 8 grains [0.32 to 0.52 Gm.]) one and one-half hours after the inception of the narcosis. The other 2 dogs were similarly killed two and one-half hours after the inception of the narcosis. The adrenal glands from the ether controls and the soluble pentobarbital controls were identical in appearance, and neither revealed any deviation from the normal appearance. Particularly noticeable was the absence of infiltration by polymorphonuclear neutrophilic leukocytes. Dunphy, Gibson and Keeley<sup>16</sup> observed mild leukocytic infiltration of the adrenal cortex following anesthesia induced with soluble pentobarbital. The

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16. Dunphy, J. E.; Gibson, J. G., II, and Keeley, J. L.: Observations on the Pathology of Experimental Traumatic Shock, Surg., Gynec. & Obst. **72**:832-833 (May) 1941.

absence of such infiltration in our controls may have been due to the fact that our control animals were killed sooner in order to correspond to the animals studied in the early period following the freeze (up to two and one-half hours).

Other microscopic changes in the anesthesia control dogs require consideration. After two and one-half hours of narcosis there were moderate capillariovenous hyperemia of the lungs, slight venosinusoidal hyperemia of the liver and focal capillariovenous hyperemia of glomerular and peritubular vessels of the kidneys. No interstitial or cellular changes were observed. These manifestations are similar to the occasional mild ones already mentioned as present in the early period following the freeze.

*Late Observations.*—Gross Examination: No serous effusions were observed. The lungs and the liver when sectioned oozed thick and dark blood. Pulmonary edema was evident grossly in a few instances. The heart ceased beating in diastole. The spleen was always firmly contracted. The intestines were as frequently relaxed as contracted. The intestinal mucosa was dark red. The adrenal cortex next to the medulla was often red.

The thawed limb was very much swollen. The edema was greatest in the subcutaneous tissues. The capillaries were extremely prominent. The soft tissues of the other limbs were pale and displayed no gross edema.

Microscopic Examination: In each case there was a distinct contrast between the picture in this late period and the early observations already mentioned. The vascular changes were everywhere marked. The venules and the capillaries of the lungs were prominent, frequently giving the alveolar wall a beaded appearance. There were capillary hemorrhages into the alveolar spaces. The evidences of alveolar edema were frequently striking, and occasionally perivascular and peribronchial edema were present. Polymorphonuclear neutrophilic leukocytes were prominent within capillaries and at times assumed an interstitial position. The capillaries and the venules of the myocardium were open diffusely. Over most fields each muscle fiber was bounded by a dilated capillary. In longitudinal section these capillaries formed streaks which frequently intercommunicated. In cross section the appearance was of a red cell partly surrounded by an endothelial cell nucleus of semilunar shape. The venosinusoidal dilatation in the liver was marked. The contraction of the spleen was evident microscopically by the small amount of blood present and the condensation of splenic corpuscles, trabeculae and pulp cells. Frequently polymorphonuclear leukocytes were more numerous than normal. The dilatation of the capillaries in the kidneys was very prominent. Most of the glomeruli became noticeable because of capillary loops that were stuffed with red cells. The



dilatation in each glomerulus was diffuse. The peritubular capillaries of both the cortex and the medulla were likewise prominent. In the medulla each tubule was flanked by a widely dilated capillary. The capillaries of the intestinal and the gastric mucosa were prominent. The appearance of these vessels in the muscles of the frozen limb resembled the description by Krogh<sup>17</sup> of muscles during marked activity.

The interstitial changes depended greatly on the organ studied. In the lung there occurred marked edema, capillary hemorrhages and interstitial infiltration with leukocytes. The liver, the kidneys and the intestinal mucosa revealed no definite interstitial changes, apparently because these regions do not have much room for the accumulation of edema fluid. The interstitial changes were greatest in the frozen limb. There was marked edema in the skin and the muscles and particularly in the subcutaneous tissue. There was precipitation of a fibrin network in this edema. Furthermore, a definite polymorphonuclear leukocytic infiltration was present; this means that the extravasation of fluid had the characteristics of an exudate.

The cellular changes were most pronounced in the liver, the kidneys, the adrenal glands and the muscle fibers of the frozen limb. Microscopic alterations of the myocardial fibers could not be identified.

Under normal conditions the hepatic cells may be lighter in staining toward the center of the lobule and much darker about the portal canals. This difference in staining is possibly associated with the distribution of glycogen in the lobule. In the late phases of freezing shock the cells stained equally throughout the lobule. There was a tendency for such cells to be darker, more granular and somewhat swollen and to have distinct cytoplasmic boundaries. These changes are considered as acute parenchymatous degeneration and depletion of glycogen. The predominance of droplets in the cytoplasm and the presence of focal areas of necrosis involving groups of three to five cells were additional cellular changes noticed in these studies. In the convoluted tubules of the kidney similar observations were made. However, the most outstanding and definite changes were seen in the zona fasciculata of the adrenal cortex. The lipid content of the cells was definitely decreased. The first indication that important changes had occurred in this layer was that it became difficult to follow the cords of cells from the zona glomerulosa all the way to the zona reticularis owing to necrobiosis of the cells and disruption of the cell cords. There were focal karyolysis and necrosis. Polymorphonuclear leukocytes were abundant. These cells accumulated about areas of necrosis and showed degenerative changes comparable to those seen about suppurative foci.

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17. Krogh, A.: *The Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1922.

In the present series these changes were greatest in the inner half of the zona fasciculata.

The muscle fibers of the frozen limb displayed loss of striation with hyalinization, fractures, marked granularity and outright necrosis.

#### RELATION OF LOSS OF PLASMA TO DAMAGE OF CAPILLARIES AND TISSUES

The pathologic changes observed may be analyzed in relation to the time and the extent of depletion of plasma or blood volume.

Figure 1 represents the relation of hemoconcentration to the time intervals in 22 dogs subjected to freezing shock. The spread in the

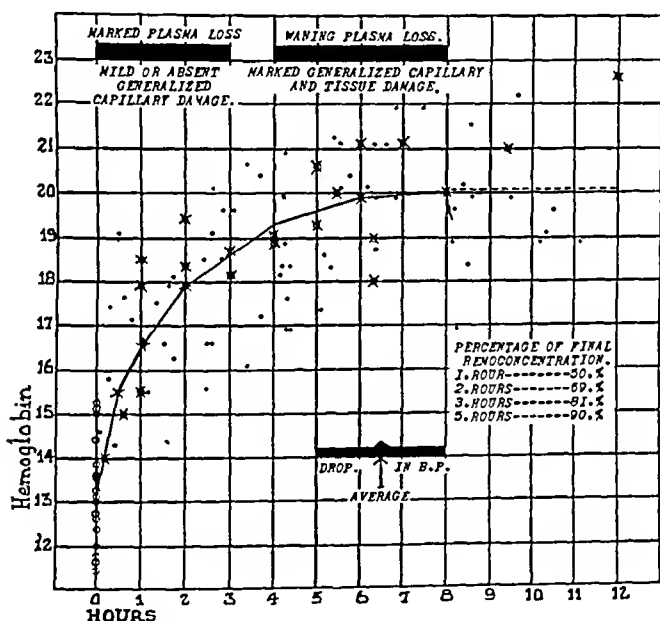


Fig. 1.—Chart showing hemoconcentration in freezing shock. The curve is an average curve taken from 106 hemoglobin values (photoelectric method expressed in grams per hundred cubic centimeters) for 22 animals shocked by the freezing procedure. The percentage of final hemoconcentration is taken to indicate the extent of loss of plasma. On such a basis it is noted that the greatest amount of loss occurs early (first three hours), when generalized capillary dilatation and parenchymatous damage are meager or absent. Hemoconcentration tends to level off or cease when the peripheral arterial pressure drops.

points from which the average curve was obtained is due to the spread of the control values. Only two curves originated below the average control hemoglobin curve and extended above the average curve. It may be argued that the early part of this curve is influenced by splenic contraction, with the release of red cells. It is conceivable that in a normal 10 Kg. dog the spleen may contain 60 to 80 cc. of blood with a

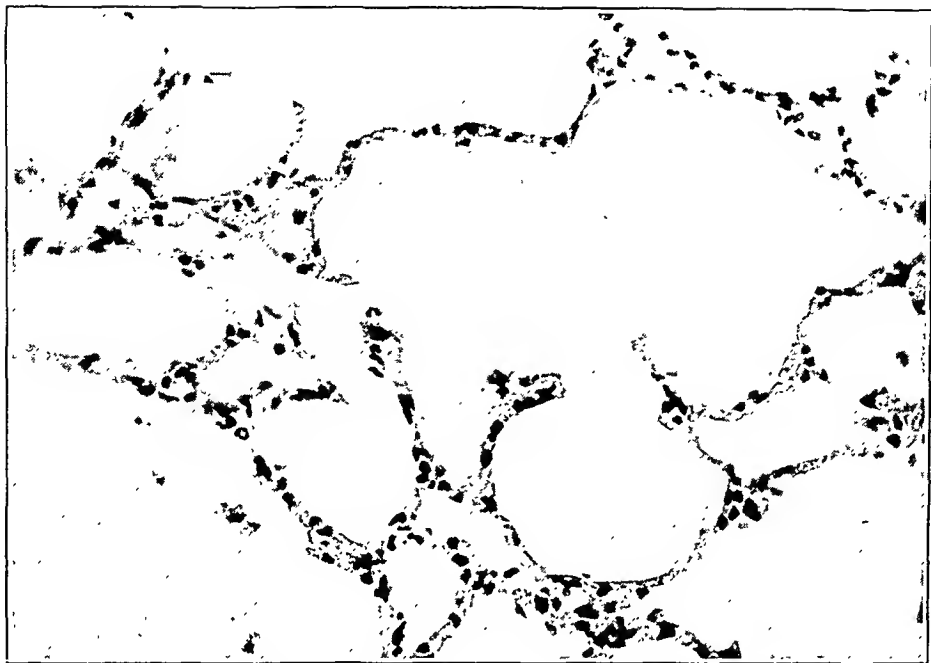


Fig. 2.—Photomicrograph of a section of a lung taken during the control period after two and a half hours of anesthesia induced with soluble pentobarbital.

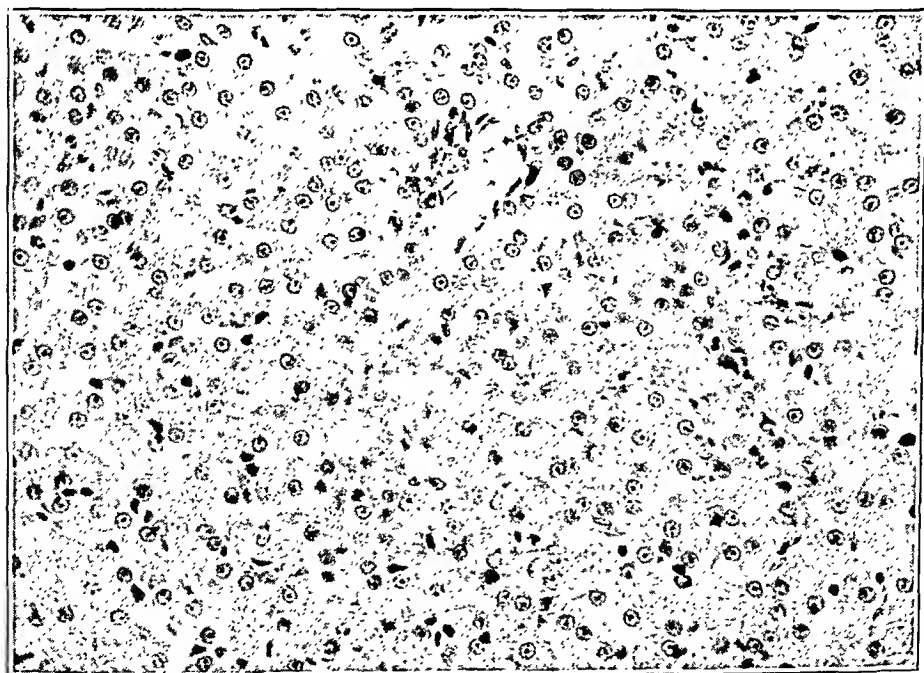


Fig. 3.—Photomicrograph of a section of the liver (central vein present) taken during the control period after two and a half hours of anesthesia induced with soluble pentobarbital.

higher hematocrit value than is present in the general circulation. Theoretically, if the entire 60 cc. were composed of red blood cells and were released to the general circulation, each point on the average curve would be higher than expected from loss of plasma alone by 1 Gm. per hundred cubic centimeters. The conformity of the curve would not change appreciably, but the per cent of the final hemoconcentration would be slightly lower for each hour if the 1 Gm. correction were made. The subsequent deductions from this curve would still hold true. Studies of plasma volume (table 2), however, indicate that added red blood cells have not influenced the curve as presented in figure 1.

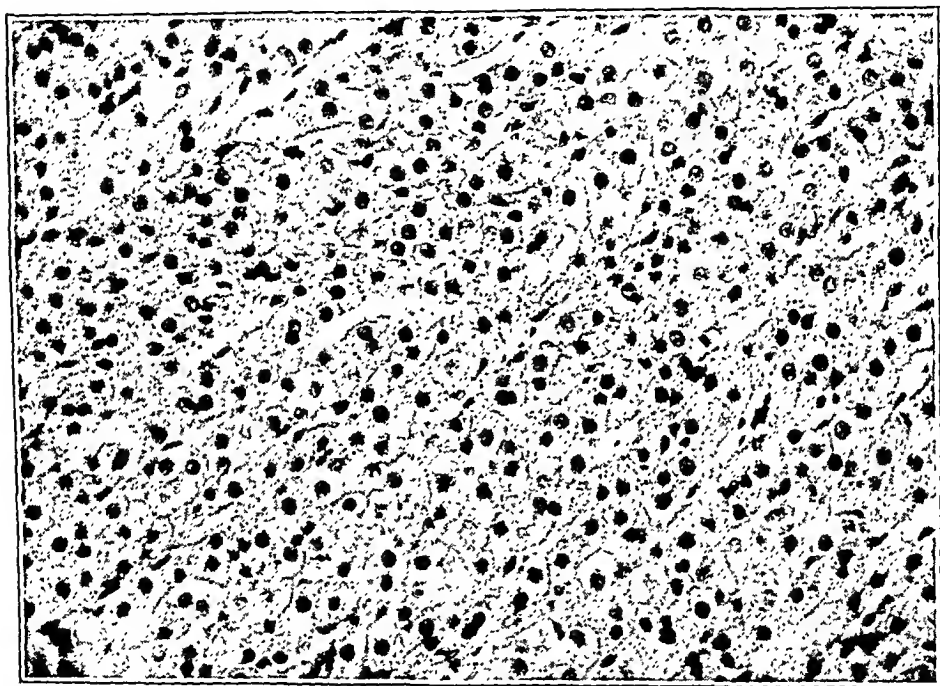


Fig. 4.—Photomicrograph of a section of the adrenal cortex (zona fasciculata) taken during the control period after two and a half hours of anesthesia induced with soluble pentobarbital.

Since in this type of shock the depletion of blood volume is strictly due to loss of plasma, the degree of hemoconcentration reflects the amount of depletion of blood volume. If one considers the final concentration of hemoglobin as 100 per cent hemoconcentration, then by considering the hourly concentration as reflected on the curve one can define the hourly percentage of final hemoconcentration. This percentage of final hemoconcentration reflects the average loss of plasma at that time. On such a basis it is striking that the loss of plasma is greatest during the first two and one-half to three hours. This is the interval during which the evidences of generalized damage to the capillaries and tissues as obtained by microscopic study are meager.

TABLE 2.—*Microscopic Observations on (a) Typical Control Dogs Killed During Anesthesia Induced with Soluble Pentobarbital; (b) Dogs Two and a Half Hours After Freeze, and (c) Dogs Four Hours or More After Freeze \**

Dog	Weight, Kg.	Comment	Period	Plasma Volume, Cc.	Hemo- globin, Gm. per 100 Cc.	Hemato- crit, per Cent	Lungs	Myo- cardium	Liver	Spleen	Kidneys	Adrenal Glands	Intestines	Frozen Leg
N.IV	11.6	Two and a half hours under anesthesia induced with soluble pentobarbital; autopsy done immediately after death	.....	...	...	...	Slight to absent capillary-venous hyperemia	Normal appearance	Slight veno-sinusoidal hyperemia	Moderate amount of blood in sinusoids	Normal appearance	Normal appearance	Normal appearance	Skeletal muscle normal in appearance
28S	10	Killed 2½ hours after freeze (early period); immediate autopsy	Control	600	12.9	...	Slight to absent capillary-venous hyperemia	Normal appearance	Moderate veno-sinusoidal hyperemia	Slight amount of blood in sinusoids	Cortex normal; slight peritubular hyperemia in medulla	Slight infiltration of cortex by leukocytes	Normal appearance	Edema and marked capillary-venous hyperemia
8S	12	Killed 4½ hours after freeze (late period); immediate autopsy	Control	...	15.3	46.5	Marked capillary-venous hyperemia; focal hemorrhages	Marked capillary-venous hyperemia	Blopsy before freeze: normal appearance. Shock period: marked veno-sinusoidal hyperemia; atrophy of cord cells; distended lymphatics	Little blood; markedly contracted	Marked capillary-venous hyperemia in glomerular and peritubular regions; no degeneration of tubular epithelium	Marked capillary hyperemia and focal hemorrhages of cortex; marked leukocytic infiltration of cortex; necrobiosis and loss of lipid of cortical cells	.....	Marked capillary-venous hyperemia and edema between fibers; loss of striations; granularity and fractures of muscle fibers
17S	9.8	Death 8 hours after freeze (late period); immediate autopsy	Control	517	13.6	43.1	Marked venous hyperemia; moderate capillary hyperemia; slight interstitial leukocytic infiltration	Marked capillary-venous hyperemia	Moderate veno-sinusoidal hyperemia; acute parenchymatous degeneration of cord cells	Marked contraction; small amount of blood	Marked cortical and medullary capillary-venous hyperemia; albuminuria; acute parenchymatous degeneration of	Marked leukocyte infiltration of cortex; degenerative changes of cortical cells (zona fasciculata and reticularis)	Marked capillary hyperemia of villi	Marked capillary-venous hyperemia and edema

\* The series included the examination of tissues from 4 normal dogs killed by fatal hemorrhage during ether anesthesia, 4 dogs killed after the induction of anesthesia with soluble pentobarbital, 6 dogs killed in the early period after the freeze (up to two and a half hours) and 8 dogs which were killed or died in the late period (beyond four hours after the freeze).

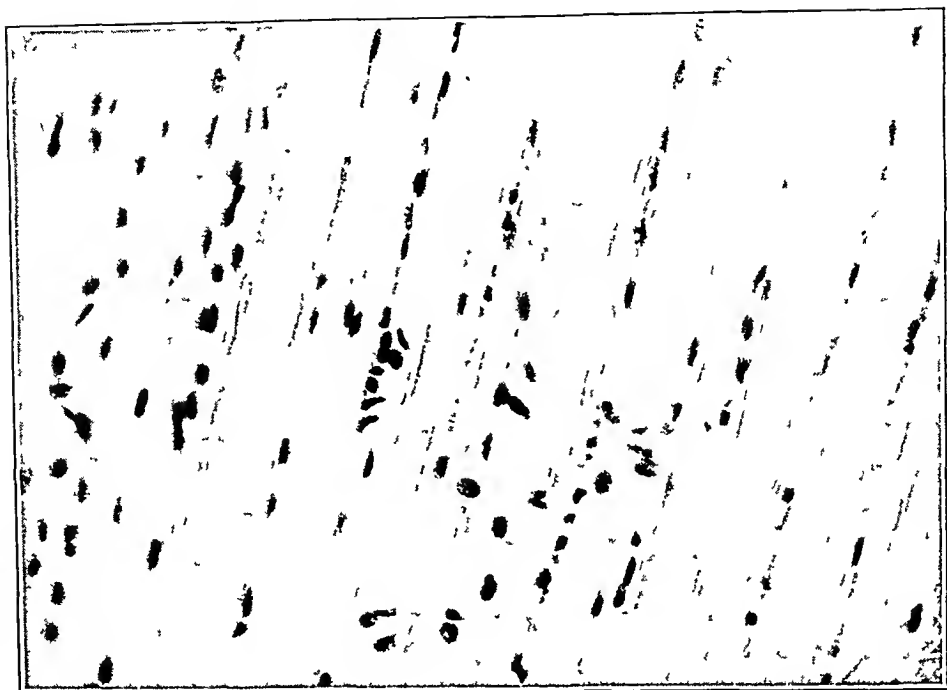


Fig. 5.—Photomicrograph of a section of skeletal muscle (lower extremity) taken during the control period after two and a half hours of anesthesia induced with soluble pentobarbital.

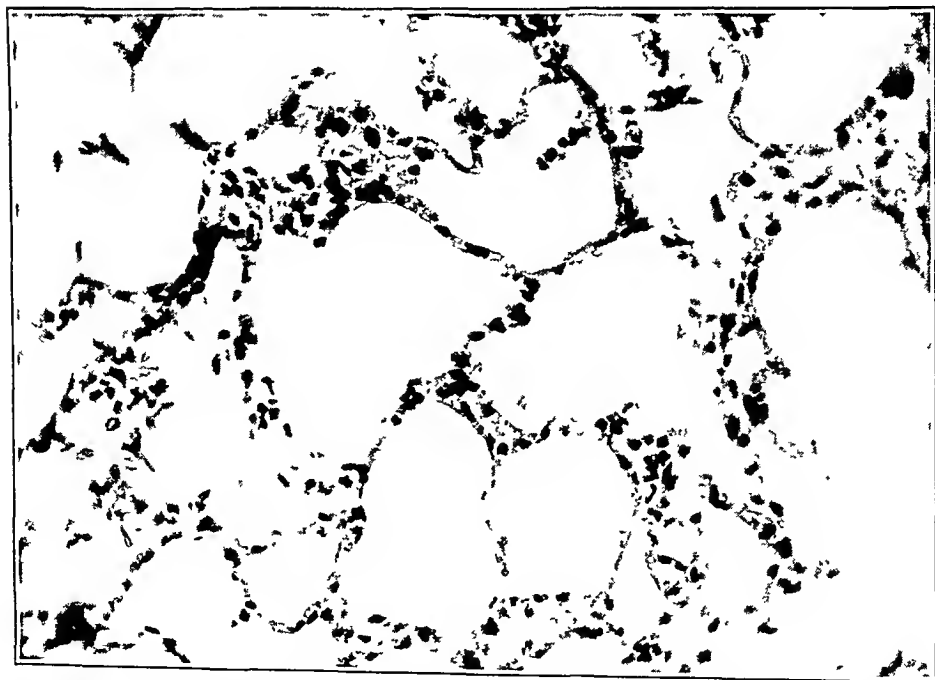


Fig. 6.—Photomicrograph of a section of a lung taken during the early period of the development of freezing shock (two and a half hours after severe freeze).

Conversely, when loss of plasma begins to wane, the generalized damage is greatest.

It is also of interest to note that in this form of shock hemoconcentration tends to reach a fairly stabilized peak at approximately six hours. This cessation of loss of plasma corresponds to the interval when the blood pressure drops markedly. The decrease in loss of plasma is partly related to a great decrease in the volume of plasma that is available. Yet on the basis of the advanced generalized damage to the capillaries hemoconcentration should continue until death.

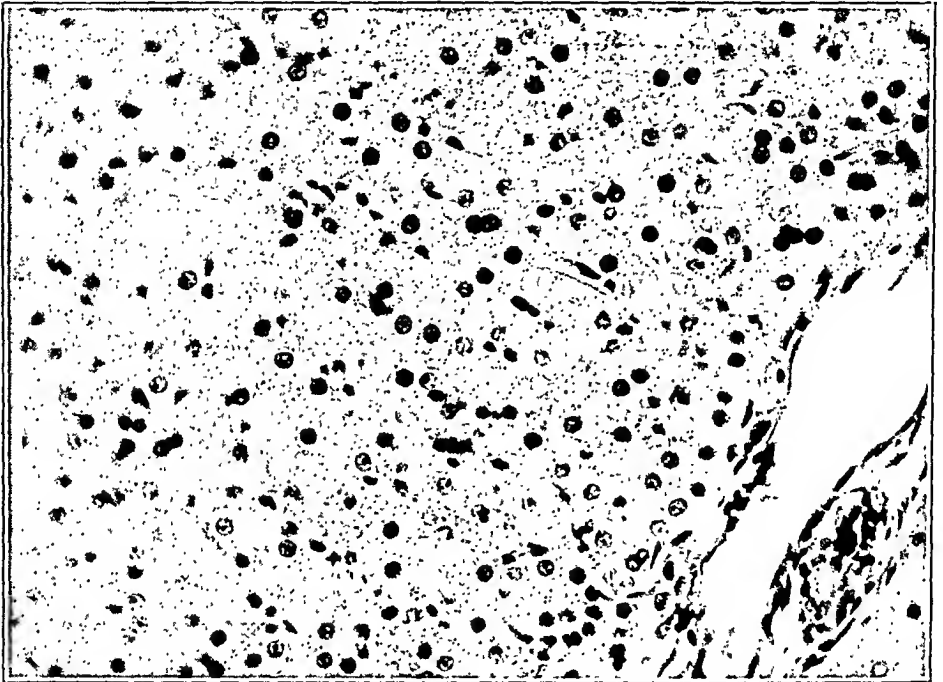


Fig. 7.—Photomicrograph of a section of the liver (near central vein) taken in the early period of the development of shock (two and a half hours after severe freeze).

The factors influencing the loss of plasma through capillaries are hydrostatic pressure in the capillaries, permeability of the walls of the capillaries, colloidal osmotic pressure of the plasma and tissue tension. The first two factors encourage the escape of plasma, whereas the last two tend to retard it. In spite of greatly damaged capillaries and no apparent change in colloidal osmotic pressure, loss of plasma may decrease markedly or cease as a result of the two other factors, viz. the building up of tension at the site of injury and the drop in peripheral arterial pressure and in capillary hydrostatic pressure. Thus, these various factors may so balance each other that the effective outgoing force is insufficient to push plasma out in spite of greatly damaged capillaries.

## CONSIDERATION OF LABORATORY TESTS USED

At the present time the various tests used in the study of distribution of fluid in this and in other forms of shock may be partly subject to criticism. Nevertheless, certain deductions can be made from the tests used, and definite trends can be developed, even if strictly quantitative interpretation may be subject to question at the present time. A partial appraisal of these tests may be obtained from the examination of possible criticisms.

It is known that the blue dye (Evans' blue) technic for determination of plasma volume may be faulty when marked endothelial damage exists.

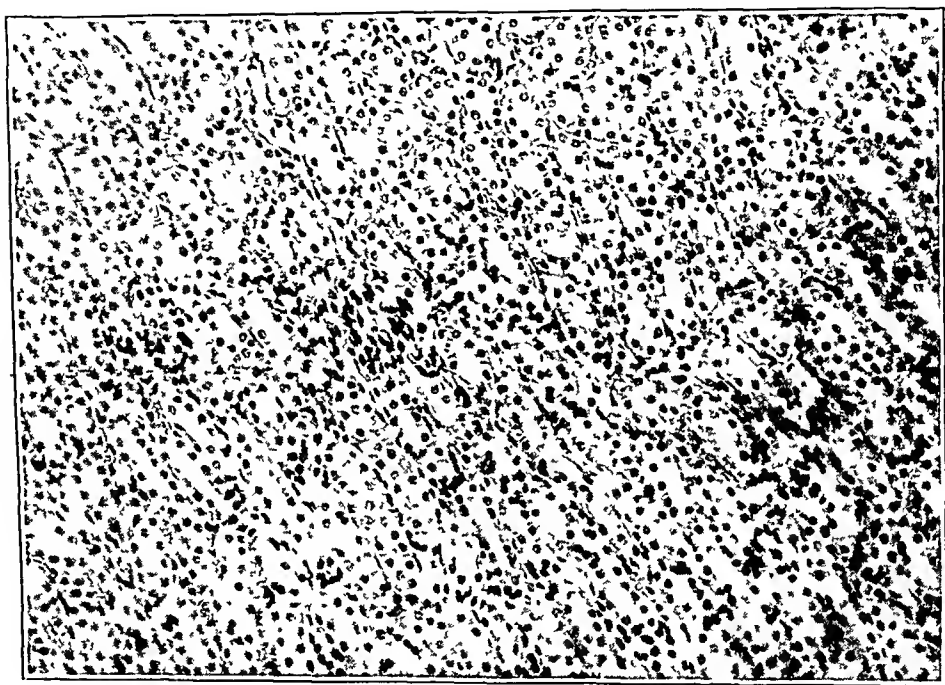


Fig. 8.—Photomicrograph of a section of kidney (medulla) taken in the early period of development of shock (two and a half hours after severe freeze).

The error may result from the loss of dye into the damaged area and from possible lack of complete mixing. These arguments are weakened by other findings. The mixing time has been found to be adequate in hemorrhagic shock.<sup>18</sup> While the loss of dye tends to make determined values for plasma volume higher than expected, in actual practice the concentration of the dye in the plasma remains so close to a stabilized point for five to fifteen minutes after thorough mixing that even with

18. Ebert, R. V.; Stead, E. A., Jr.; Warren, J. V., and Watts, W. E.: Plasma Protein Replacement After Hemorrhage in Dogs With and Without Shock, *Am J. Physiol.* **136**:299-305 (April) 1942.



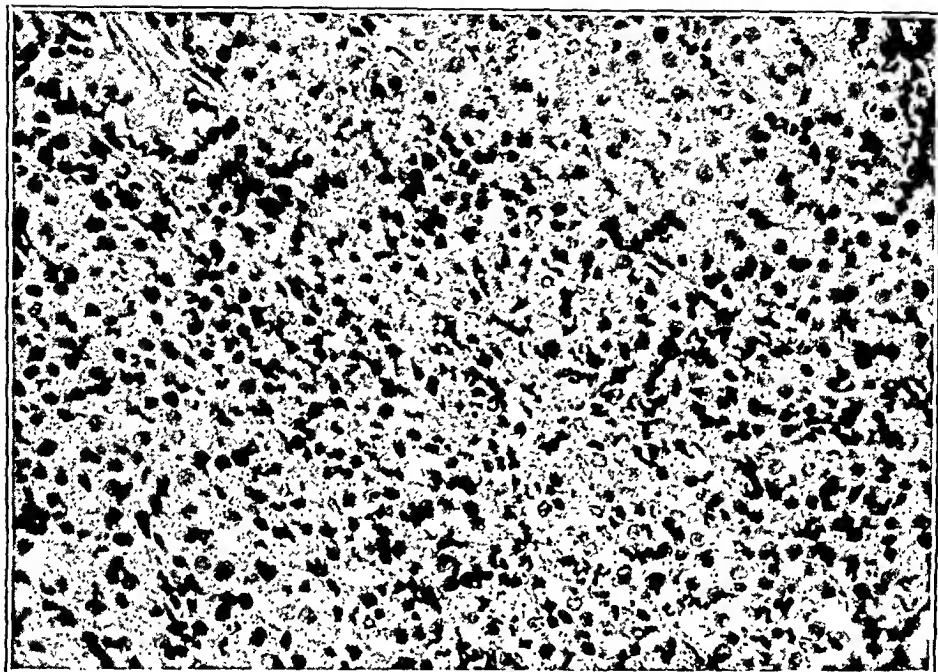


Fig. 9.—Photomicrograph of a section of the adrenal cortex (zona fasciculata) taken in the early period of development of shock (two and a half hours after severe freeze). Notice the prominent infiltration of polymorphonuclear neutrophilic leukocytes.



Fig. 10.—Photomicrograph of a section of skeletal muscle (lower extremity, site of freeze) taken in the early period of development of shock (two and a half hours after severe freeze). Notice the prominent dilatation of capillaries with the packing of masses of red blood cells (stasis) and the edema causing a spreading of the muscle fibers. An occasional neutrophilic leukocyte is seen in an interstitial location.

a more rapid loss the final determination of plasma volume gives a result that tallies close to that expected when no endothelial damage exists. Table 3 exemplifies this point. The concentration of the dye was recorded at various intervals during the control period and after the animal was in deep and late shock.

The blue dye method, then, seems to serve as a good index of the degree of decrease of plasma volume, and at the same time it serves as a means of estimating the amount of total protein lost from the circulation during freezing shock.

The two methods that have been used to determine changes in the amount of extracellular water are the thiocyanate method and the determination of the plasma sodium concentration. The latter is made possible by the concept that the sodium ion does not pass through

TABLE 3.—*Concentration of Dye in a Dog at Various Intervals During Control and Shock Periods\**

Dog	Weight, Kg.	Period	Minutes After Injection	Plasma Volume, Cc.	Blood Pressure, Mm. of Hg	Concentration of Dye, Mg./100 Cc.
27S	10	Control	10	660	165	0.91
		Control	24	...	...	0.91
		Control	41	...	...	0.85
		Shock	10	291	78	2.06
		Shock	19	...	73	2.06
		Shock	30	...	60	1.97

\* Note that there is no perceptible difference in the concentration of blue dye for ten to fourteen minutes after thorough mixing. The disappearance of the dye from the plasma is more rapid during shock. On each occasion (control and shock) 6 mg. of Evans' blue dye was injected intravenously.

cellular membranes.<sup>19</sup> In an acute experiment an increase in sodium ion concentration is taken to represent a loss of water from the extracellular compartment without a corresponding loss of sodium. It is not known as yet how valid the thiocyanate method is in severe and late shock. It appears logical to assume that if the changes in sodium ion concentration correspond to the results obtained by the thiocyanate method the latter method is as dependable in late shock as in normal or near-normal circulatory conditions. Such a correlation has been observed in these studies.

It is evident that these tests have at present a somewhat ill defined status, and one may be hesitant to draw clearcut conclusions from them, but they at least serve to indicate qualitative trends. These trends

19. Gilman, A.: Experimental Sodium Loss Analogous to Adrenal Insufficiency: The Resulting Water Shift and Sensitivity to Hemorrhage, *Am. J. Physiol.* **108**:662-669 (June) 1934. Peters, J. J.: Water Balance in Health and in Disease, in Duncan, G. G.: *Diseases of Metabolism*, Philadelphia, W. B. Saunders Company, 1942, chap. 6, pp. 270-350.

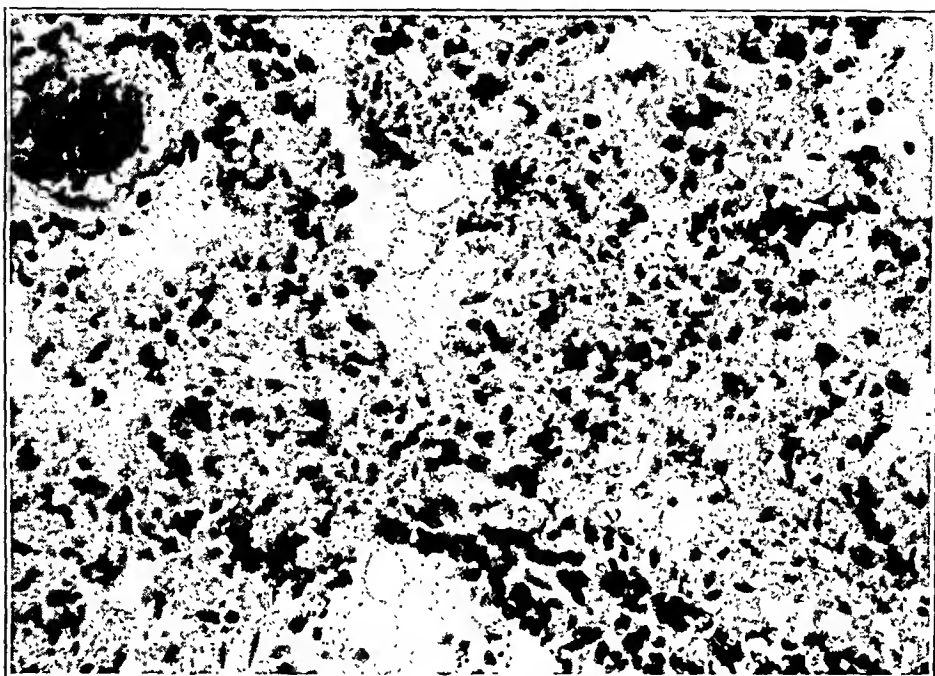


Fig. 11.—Photomicrograph of a section of a lung taken during shock (late period) over four hours after severe freeze. Marked capillariovenous hyperemia, capillary hemorrhages and edema are present.

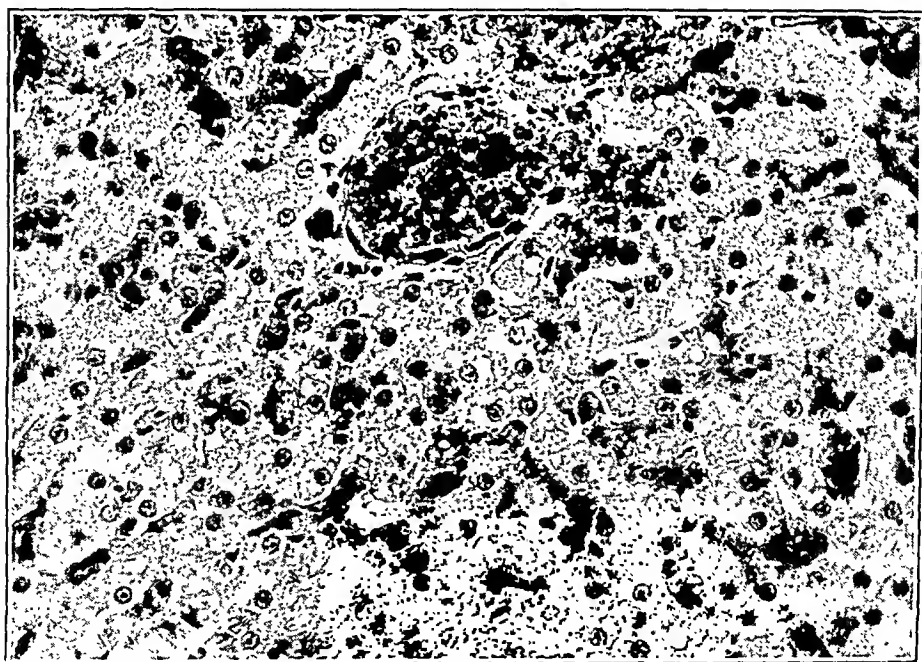


Fig. 12.—Photomicrograph of a section of the liver (near central vein) taken during shock (late period) over four hours after severe freeze. Marked venosinoidal hyperemia and droplet degeneration of cytoplasm are present.

suggest that in late freezing shock there are a pronounced decrease in plasma volume, a pronounced decrease in total circulating protein and a decrease in both the extracellular and the interstitial fluid volume. It would also seem logical to assume that the decrease in extracellular volume results from the passage of water into body cells, since no other easily accessible reservoir is available. In a future publication<sup>5</sup> data indicating that this misplaced water is available for increase in plasma volume following treatment with concentrated protein solutions will be discussed.

The samples of plasma taken for study after the freeze were invariably stained with free hemoglobin. The staining was greatest

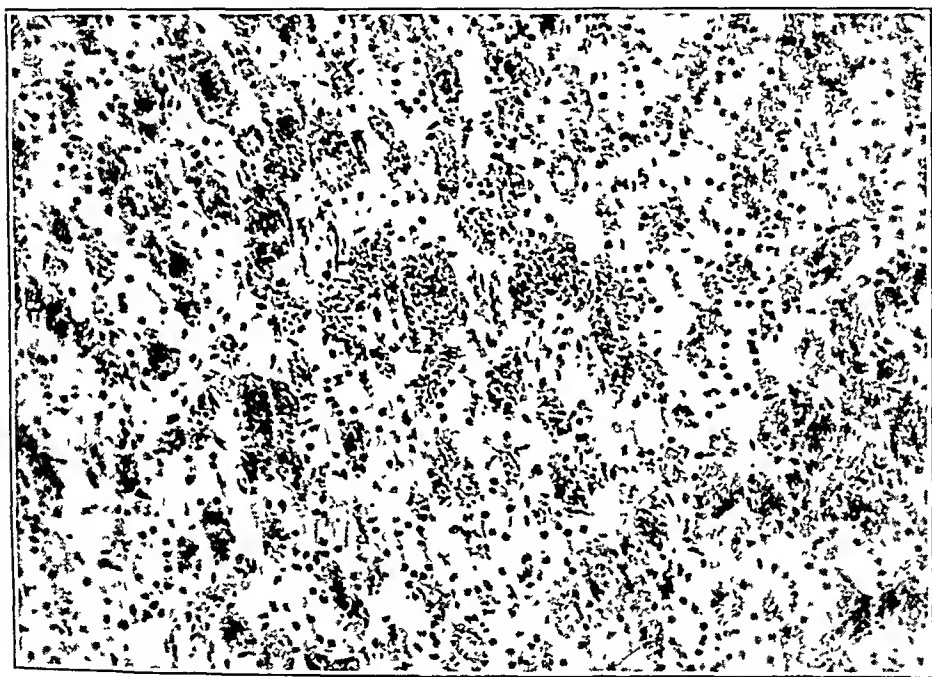


Fig. 13.—Photomicrograph of a section of the kidney (medulla) taken during shock (late period) over four hours after freeze. There is marked capillary hyperemia.

during deep and late shock. Control samples never revealed such staining. When determinations of plasma hemoglobin<sup>20</sup> were carried out, it was observed that the hemoglobin concentration remained the same at intervals of several minutes over a period of one hour. It was also noticed that the control sample for the determination with Evans' blue dye could be set at 100 in the colorimeter and that samples taken

20. Bing, F. C., and Baker, R. W.: The Determination of Hemoglobin in Minute Amounts of Blood by Wu's Method, *J. Biol. Chem.* **92**:589-600 (Aug.) 1931.

after the injection of the dye could be read as usual in the photoelectric colorimeter without the need for using special filters and equations such as are commonly employed to correct for the effects of the staining of the plasma with hemoglobin.

The liberation of free hemoglobin did not seem to be due to the breaking up of fragile cells as they were jammed into the narrow orifice of the venipuncture needle. This was demonstrated when hemoglobin-containing plasma was obtained by bleeding from the carotid artery directly into a test tube and immediately centrifuging the sample.

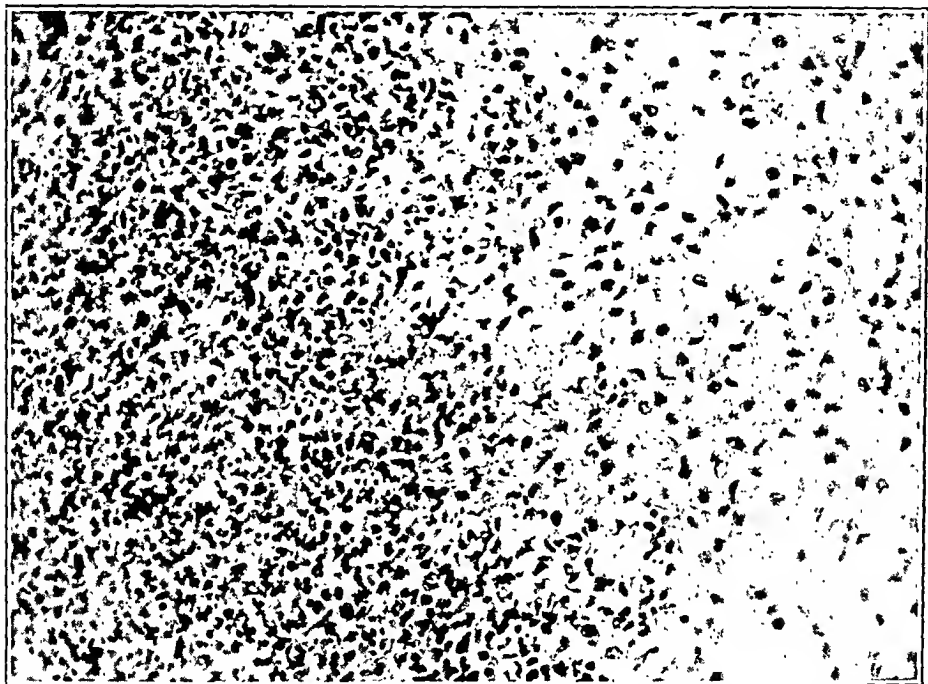


Fig. 14.—Photomicrograph of a section of the adrenal cortex (zona fasciculata) taken during shock (late period) over four hours after severe freeze. There is necrosis of the zona fasciculata with a bordering zone of leukocytic infiltration.

It was considered, then, that hemoglobinemia occurred after the freeze. The most logical source seemed to be the frozen limb, since one of the most rapid methods of artificially producing hemolysis is by freezing and thawing whole blood *in vitro*. Since the apparent hemoglobinemia was greatest during the late phase of shock and since it had been observed by us in traumatic shock, it was considered that other factors operated to produce an intravascular liberation of hemoglobin from red blood cells. Whether the element of stasis within capillaries during shock is conducive to this phenomenon can be considered only through reasoning by analogy. Stasis of red blood cells in the spleen

has been considered to produce spheroidicity, increased fragility and possible *in vivo* hemolysis.<sup>21</sup> Coonse, Foisie, Robertson and Aufranc<sup>22</sup> also observed *in vivo* hemolysis during traumatic shock in animals.

The pathologic changes seen microscopically were compared with observations on control animals subjected to uncomplicated soluble pentobarbital anesthesia and on controls killed by a fatal hemorrhage after a few minutes of deep ether anesthesia. Blalock<sup>23</sup> discussed the histologic changes following prolonged periods of various types of experimental anesthesia. Such changes resemble in certain respects the vascular manifestations in late shock. Moon<sup>24</sup> emphasized the role of



Fig. 15—Photomicrograph of a section of skeletal muscle (lower extremity, site of freeze) taken during shock (late period) over four hours after freeze. Marked capillary and venous stasis, edema and necrosis of muscle fiber. Notice the close resemblance to figure 10.

21. Ham, T. H., and Castle, W. B.: Studies on Destruction of Red Blood Cells: Relation of Increased Hypotonic Fragility and of Erythrostatics to the Mechanism of Hemolysis in Certain Anemias, *Proc. Am. Phil. Soc.* **82**:411-419 (May) 1940; abstracted in Minot, G. R., and Castle, W. B.: *Year Book of General Medicine*, Chicago, The Year Book Publishers, Inc., 1940, pp. 365-367.

22. Coonse, G. K.; Foisie, P. S.; Robertson, H. F., and Aufranc, O. E.: Traumatic and Hemorrhagic Shock: Experimental and Clinical Study, *New England J. Med.* **212**:647-663 (April 11) 1935.

23. Blalock, A.: Shock: Further Studies with Particular Reference to Effects of Hemorrhage, *Arch. Surg.* **29**:837-857 (Nov.) 1934.

24. Moon, V. H.: *Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938.

anesthetic agents in modifying the late pathologic changes caused by shock. In our present studies we feel justified in separating the early from the late observations because the differences were so clearcut. The fact that the early vascular changes and those of the anesthesia control dogs resembled each other is further evidence in favor of the meagerness or absence of generalized capillariovenous changes during the period of greatest loss of plasma. Since normal dogs invariably recover successfully from the doses of soluble pentobarbital used in the present studies and since following freezing there was invariably progressive and fatal shock, the pathologic changes of the late period must have been due to the shock and its complications.

#### COMMENT

In these studies on shock following freezing (thermal injury) there was a difference between the period of greatest loss of plasma and the period of marked damage to the capillaries and tissues. This is in accord with the observations on the thermal injury due to burns recorded by Dunphy, Gibson and Keeley.<sup>16</sup> However, as was pointed out by these authors, it does not mean that under different circumstances shock cannot be due to generalized capillary (endothelial) damage. Moon<sup>25</sup> demonstrated that deficit of blood volume with hemoconcentration associated with certain toxic agents (such as histamine) is the result of generalized loss of plasma through damaged capillaries. Nevertheless, when the local damage is such as to give rise to a rapid local loss of plasma without any complicating hemorrhage, the generalized damage to capillaries and tissues seems to be secondary. The latter events occur after a severe freeze and are concordant with the contentions of Blalock<sup>26</sup> concerning other shock-producing injuries associated with prominent local loss of fluid.

It has been confusing to us in the past to observe waning hemoconcentration during the period when damage to the capillaries was supposedly greatest (late shock). In these studies, this definite stabilization of hemoconcentration (loss of plasma) was directly related to the interval when the peripheral arterial blood pressure dropped. This correlation has led to the conclusion that the hydrostatic pressure in the capillaries was insufficient to force plasma out in spite of severe damage to the capillaries. Tension in the tissues at the site of the freeze may influence the loss of plasma in the later periods. That this

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25. Moon, V. H.: The Vascular and Cellular Dynamics of Shock, *Am. J. M. Sc.* **203**:1-18 (Jan.) 1942; footnote 24.

26. Blalock, A.: *Principles of Surgical Care: Shock and Other Problems*, St. Louis, C. V. Mosby Company, 1940.

is not the only factor involved, however, is demonstrated by the increase in weight and size of the damaged limb following therapy with solutions of sodium chloride or with dilute serum.<sup>5</sup>

After hemorrhage the blood volume may be adequately maintained by the passage of fluid from the tissues (interstitial and/or cellular compartments) into the blood stream.<sup>27</sup> Moon and associates<sup>28</sup> demonstrated outstanding hemodilution and a decrease of the fluid content of certain tissues in the body when large volumes of blood were removed from dogs over periods up to fifty-four hours. On the other hand, if the blood volume is allowed to remain sufficiently depleted over a period of a few hours by repeated bleedings alone, hemoconcentration<sup>29</sup> and damage to the capillaries can occur.<sup>30</sup> The degree of hemoconcentration may be influenced by the hydrostatic pressure in the capillaries at the time when the endothelial damage is sufficient to allow the escape of plasma.

The loss of plasma with hemoconcentration associated with large hemorrhages does not seem to be so much dependent on how long the blood pressure is depressed or how much blood is removed as on how long the circulating blood volume is allowed to remain critically depleted. Therefore, if after each bleeding sufficient time is allowed for the intruding tissue fluid to swell the blood volume above the critical level, hemoconcentration and shock need not develop at all, but instead outstanding hemodilution will result.

The foregoing analysis is once more presented to emphasize the necessity of the maintenance of the circulating volume in the treatment of shock rather than the maintenance of any particular constituent of blood, such as the red blood cells. Similarly, prevention of hemorrhagic

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27. (a) Adolph, E. F.; Gerbon, M. J., and Lepore, M. J.: The Rate of Entrance of Fluid into the Blood in Hemorrhage, *Am. J. Physiol.* **104**:502-517 (May) 1933. (b) Stewart, J. D., and Rourke, G. M.: Intracellular Fluid Loss in Hemorrhage, *J. Clin. Investigation* **15**:697-702 (Nov.) 1936. (c) Lands, A. M., and Johnson, W.: Distribution of Body Water Following Hemorrhage, *Proc. Soc. Exper. Biol. & Med.* **49**:123-128 (Feb.) 1942.

28. Moon, V. H.; Morgan, D. R.; Lieber, M. M., and McGrew, D.: Similarities and Distinctions Between Shock and the Effects of Hemorrhage, *J. A. M. A.* **117**:2024-2030 (Dec. 13) 1941.

29. (a) Blalock, A.: Acute Circulatory Failure as Exemplified by Shock and Hemorrhage, *Surg., Gynec. & Obst.* **58**:551-566 (March) 1934. (b) Davis, H. A., cited by Harkins.<sup>30</sup> (c) Muirhead, E. E.; Ashworth, C. T., and Hill, J. M.: The Therapy of Shock in Experimental Animals with Plasma Protein Solutions: I. Concentrated Plasma as a Hemodiluting Agent, *Surgery* **12**:14-23 (July) 1942.

30. Harkins, H. W.: Recent Advances in the Study and Management of Traumatic Shock, *Surgery* **9**:231-294 (Feb.) 1941. Blalock,<sup>29a</sup> Davis,<sup>29b</sup>



shock with extreme hemodilution can be accomplished by the proper use of solutions of concentrated plasma<sup>31</sup> with practically no risk of critical anemic anoxemia.

The importance of the depleted blood volume,<sup>32</sup> the decreased venous return to the heart and central effective venous pressure,<sup>33</sup> the decreased cardiac output,<sup>34</sup> the alterations of peripheral blood flow<sup>35</sup> and other changes in hemodynamics associated with shock have been justly emphasized. It appears that insufficient emphasis has been placed on the possible abnormal shifts of fluid between the plasma, interstitial and cellular fluid compartments in shock and during its pathogenesis. This is surprising, since Moon<sup>36</sup> observed an increase in the fluid content of tissue during shock and Davis<sup>37</sup> noted that the viscera weighed more when patients died after a period of shock. Ashworth and Kregel<sup>38</sup> observed abnormalities in distribution of fluid and in electrolytic balance associated with posthemorrhagic shock and with shock following the intraperitoneal injection of hypertonic solution of sodium chloride. In the severe posthemorrhagic type the interstitial fluid volume decreased, and this was considered to be due to the shifting of fluid into an abnormal location, such as body cells. In the other type of shock an increase in interstitial fluid was observed. This was interpreted to represent a pronounced increase in concentration of extracellular sodium which caused a shift of fluid out of body cells. The present study on freezing shock indicates not only a decrease in plasma

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31. (a) Hill, J. M.; Muirhead, E. E.; Ashworth, C. T., and Tigertt, W. D.: The Use of Desiccated Plasma with Particular Reference to Shock, *J. A. M. A.* **116**:395-402 (Feb. 1) 1941. (b) Muirhead, E. E., and Hill, J. M.: The Advantages and Clinical Uses of Desiccated Plasma Prepared by the Adtevac Process, *Ann. Int. Med.* **16**:286-302 (Feb.) 1942.

32. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Hemorrhage, Medical Research Committee, Special Report Series, no. 27, London, His Majesty's Stationery Office, 1919.

33. Wiggers, C. J.: The Present Status of the Shock Problem, *Physiol. Rev.* **22**:74-123 (Jan.) 1942.

34. Johnson, G. S., and Blalock, A.: Experimental Shock: Study of Effects of Hemorrhage, of Trauma to Muscles, of Trauma to Intestines, of Burns and of Histamine on Cardiac Output and on Blood Pressure of Dogs, *Arch. Surg.* **23**:855-863 (Nov.) 1931.

35. Cullen, M. L.; Schecter, A. E.; Freeman, N. E., and Laws, M. K.: The Circulation in Traumatic Shock, in Mudd, S., and Thalhimer, W.: *Blood Substitutes and Blood Transfusion*, Springfield, Ill., Charles C. Thomas, Publisher, 1942.

36. Moon (footnotes 24 and 25).

37. Davis, H. A.: Pathology of Shock in Man: Visceral Effects of Trauma, Hemorrhage, Burns and Surgical Operations, *Arch. Surg.* **41**:123-146 (July) 1940.

38. Ashworth, C. T., and Kregel, L. A.: Changes in the Body Water Partition and Extracellular Electrolytes in Shock, *Arch. Surg.* **44**:829-839 (May) 1942.

but also a depletion of the interstitial fluid, which seems to suggest a shift of fluid into cells, particularly in the late phases of such shock. Such changes are important because they are directly related to the treatment of shock. It is generally agreed that proper intravenous administration of fluid offers more in the prevention and the treatment of shock than any other single procedure. The intravenous injection of a solution that instead of remaining within blood vessels passes into the tissues merely accentuates the abnormal distribution of fluid present. Conversely, a solution capable of shifting the misplaced fluid into the blood stream and retaining it there not only increases a depleted blood volume but at the same time reverses one of the abnormalities present. There are indications that in normal animals concentrated serum is capable of mobilizing cellular fluid.<sup>39</sup> Evidence supporting the occurrence of a similar shift in late freezing shock will be presented later.<sup>5</sup>

In the histologic observations made in the present study outstanding lesions were related to the adrenal cortex, particularly the zona fasciculata. Such lesions have been emphasized by Dunphy, Gibson and Keeley<sup>16</sup> and others.<sup>40</sup> The former authors reported slight but similar changes in the adrenal cortex following anesthesia induced with soluble pentobarbital. We have been unable to observe such changes after one and one-half and two and one-half hours of similar anesthesia. The role of the lesions in the adrenal cortex in the shock syndrome is not known. Adrenal cortical extract has been administered in cases of shock, partly because such lesions have been observed, partly because of its apparent action on endothelial permeability and tone of the capillaries and partly because of the elevation in the potassium content of the plasma in the late phase of shock. The effect of the synthetic preparation desoxycorticosterone acetate on capillary permeability has been questioned.<sup>41</sup> However, clinically, beneficial results have been observed from the use of cortical extract.<sup>42</sup> Certain questions concerning this problem require reexamination. First, is the possible decrease in distribution of the hormone of the adrenal cortex due to

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39. Ashworth, C. T.; Muirhead, E. E., and Hill, J. M.: The Effect of Hypertonic Plasma on the Body Fluids in Normal Experimental Animals, *Am. J. Physiol.* **136**:194-199 (March) 1942.

40. Davis, H. A.: Pathology of Dehydration Shock, *Arch. Surg.* **42**:939-955 (May) 1941. Duncan, G. W., and Blalock, A.: The Uniform Production of Experimental Shock by Crush Injury: Possible Relationship to Clinical Crush Syndrome, *Ann. Surg.* **115**:684-697 (April) 1942. Davis.<sup>37</sup>

41. Fine, J., and Fischmann, J.: A Study of the Effect of Desoxycorticosterone Acetate on Capillary Permeability, *Proc. Soc. Exper. Biol. & Med.* **49**:98-102 (Jan.) 1942.

42. Rhoads, J. E.; Wolff, W. A., and Lee, W. E.: The Use of Adrenal Cortical Extract in the Treatment of Traumatic Shock of Burns, *Ann. Surg.* **113**:955-968 (June) 1941.

a decrease in its production as indicated by the cortical lesions, or is it due to a lack of distribution attended by a stagnant circulation? Second, are the beneficial results produced by administration of adrenal cortical extract due not only to its action on endothelial permeability and capillary tone but also to its influence on cellular water? It has been considered that in the crisis of Addison's disease (clinical or experimentally produced) there is a shift of water into cells which is reversed when adrenal cortical extract is administered. If such questions were answered, this treatment for shock might be established on a firmer basis.

### SUMMARY AND CONCLUSIONS

A severe freeze of one entire hindlimb of a dog is a reliable and simple method of producing a rapid and pronounced loss of plasma volume (blood volume) in an experimental animal without complicating hemorrhages. Thawing is complete in one to one and one-half hours at room temperature, and the procedure leads regularly to severe and fatal shock within six to twelve hours.

The greatest loss of plasma volume occurred within the two and one-half hours immediately following the freeze (early period). This was the interval when generalized damage to the capillaries of the viscera was mild or absent and did not differ materially from the slight dilatation of the capillaries occasionally observed during the same interval in animals under uncomplicated anesthesia induced with soluble pentobarbital U. S. P. (pentobarbital sodium). Generalized interstitial and cellular changes were not observed to occur in this period.

During this early period the only outstanding pathologic changes were in the frozen and thawed limb and in the adrenal cortex (zona fasciculata). The early lesions in the latter were a decrease in lipid content and prominent infiltration by polymorphonuclear neutrophilic leukocytes.

After the fourth hour (late period) the loss of plasma decreased greatly, but generalized capillariovenous dilatation was marked. In this interval pulmonary edema, capillary hemorrhages, leukocytosis and cellular changes in parenchymatous organs became evident.

The stabilization of the hemoconcentration in spite of evidences of generalized damage to the capillaries was directly associated in time with the drop in the peripheral arterial pressure.

Studies on hemoconcentration, plasma volume, total circulating proteins, carbon dioxide-combining power of the plasma, water available for the solution of sodium thiocyanate and plasma sodium concentration gave rise to certain interesting observations. There was an extreme depletion of plasma volume and total circulating proteins, which was paralleled by the hemoconcentration. The carbon dioxide-combining

power of the plasma was greatly decreased. The water available for the solution of thiocyanate (extracellular) was decreased, with a corresponding increase in plasma sodium concentration. In view of the observations by others suggesting an increase in tissue fluids in other forms of shock, these two findings are interpreted as representing the passage of water into body cells.

On the basis of definite staining of the samples of plasma with hemoglobin, hemoglobinemia was considered to be present. The possible causes for this phenomenon are discussed.

Certain therapeutic applications of these observations are presented.

The possible role of the hormone of the adrenal cortex and its theoretic relation to the changes produced by shock are briefly mentioned.

Miss Mary Seaman prepared all of the tissue sections (approximately 300 blocks) and Miss Frances Jones determined the carbon dioxide-combining power of the plasma. The other procedures were performed by us.

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# EXPERIMENTAL GAS GANGRENE

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The purpose of this paper is to report a series of experiments with animals carried out in order to evaluate the effectiveness of the local application of certain of the newer chemotherapeutic agents in fresh traumatic wounds contaminated with the species of clostridia commonly associated with clinical gas gangrene in human beings.

While there are already considerable data along these lines, the results of the experiments reported in the literature have not been uniform, and there are differences of opinion among various observers as to the merit of chemotherapy in relation to the prevention and the treatment of these infections.

## REVIEW OF THE LITERATURE

The first article dealing with the use of sulfonamide compounds in the treatment of gas gangrene in experimental animals was that of Domagk<sup>1</sup> in 1937. He produced gas gangrene in mice by the intramuscular injection of *Clostridium septicum* and treated the animals with certain of the sulfonamide compounds (sulfanilamide, sulfanilylsulfanilamide, sulfanilyl-monomethylsulfanilamide, and sulfanilyldimethylsulfanilamide) given orally. Sulfanilamide was ineffective, but in some experiments with the other three compounds as high as 70 per cent of the treated animals survived. Domagk stated that with *Clostridium welchii* less favorable results were obtained. About the same time Long and Bliss<sup>2</sup> reported that they were able to protect mice against intraperitoneal injection of *Cl. welchii* by means of oral administration of sulfanilamide commenced one hour after the injections. Of the treated animals 72 per cent survived, as compared with 7 per cent of the controls. Using mice,

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1. Domagk, G.: Weitere Untersuchungen über die chemotherapeutische Wirkung sulfonamidhaltiger Verbindungen bei bakteriellen Infektionen, *Klin. Wchnschr.* **16**:1412-1418 (Oct. 9) 1937.

2. Long, P. H., and Bliss, E. A.: Observations upon the Experimental and Clinical Use of Sulphanilamide in the Treatment of Certain Infections, *Canad. M. A. J.* **37**:457-465 (Nov.) 1937.

Natvig<sup>3</sup> injected 0.1 cc. of twenty-four hour cultures of *Cl. welchii*, *Clostridium histolyticum*, *Cl. septicum* and *Clostridium novyi* intramuscularly into one buttock and different amounts of azosulfamide<sup>4</sup> into the other. No protection was observed. All of the treated as well as all of the control animals died from gas gangrene within one to two days. Another unfavorable report came from Kendrick,<sup>5</sup> who worked with guinea pigs and produced gas gangrene by the intramuscular injection of *Cl. welchii*. Sulfanilamide was administered by mouth, subcutaneously and intraperitoneally; azosulfamide was given subcutaneously, and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was given by mouth. None of the drugs was found to be effective. On the other hand, considerable success was obtained by the use of antitoxin. Johnson and Meleney<sup>6</sup> studied the action in vivo of zinc peroxide on *Cl. welchii*. Organisms from an eighteen hour culture mixed with zinc peroxide suspension immediately before use were injected into the thigh muscles of guinea pigs. Of 18 animals thus treated 94 per cent survived, whereas none of the control animals survived.

Early in 1940 there appeared a succession of papers dealing with the chemotherapy of experimental gas gangrene. Stephenson and Ross<sup>7</sup> studied the effect of orally or subcutaneously administered sulfanilamide and sulfapyridine and antitoxic serum on *Cl. welchii*, *Cl. septicum* and *Cl. novyi* infections produced in mice by either intraperitoneal or intramuscular injections of suspensions of vegetative organisms in sterile garden soil. These authors concluded that when *Cl. welchii* was injected intraperitoneally sulfanilamide and sulfapyridine protected against a small number of lethal doses. On the other hand, when the injection was intramuscular, the drugs were of value only against a sublethal dose. In the animals inoculated intraperitoneally treatment with serum was effective for a strain of high toxigenicity but failed against a strain of low toxigenicity but higher invasiveness. For the group of animals given intramuscular injections serum treatment was better than drug therapy.

3. Natvig, H.: Experimental Investigations on Effect of Prontosil in Gas Gangrene, *Norsk mag. f. lægevidensk.* **99**:631-635 (June) 1938.

4. Azosulfamide is disodium-4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxy-naphthalene-3',6'-disulfonate. This substance has been known as prontosil soluble, as prontosil and as neoprontosil.

5. Kendrick, D. B., Jr.: Treatment of Gas Gangrene Infections in Guinea Pigs with Neoprontosil, Sulfanilamide, and Sulfapyridine: An Experimental Study, *J. Clin. Investigation* **18**:593-596 (Sept.) 1939.

6. Johnson, B. A., and Meleney, F. L.: The Antiseptic and Detoxifying Action of Zinc Peroxide on Certain Surgical Aerobic, Anaerobic, and Microaerophilic Bacteria, *Ann. Surg.* **109**:881-911 (June) 1939.

7. Stephenson, D., and Ross, H. E.: The Chemotherapy of *Cl. Welchii* Type A and *Cl. Septique* Infections in Mice, *Brit. M. J.* **1**:471-475 (March 23) 1940.

Sulfanilamide had little influence on infections produced with *Cl. septicum*. Sulfapyridine was better and in large doses saved 50 per cent of the animals. Treatment with a single dose of antitoxic serum was at least as effective as sulfapyridine. However, the best results were obtained by a combination of sulfapyridine and serum. Neither of the drugs had any influence on the course of infection with *Cl. novyi*. Henderson and Gorer<sup>8</sup> found that sulfapyridine by mouth was effective when vegetative forms of *Cl. welchii* or spores of *Cl. septicum* were introduced into mice by intradermal injection but that it was unreliable against intramuscular injections. The results against *Cl. welchii* were much less striking than those against *Cl. septicum*. Sulfanilamide was found to be markedly inferior to sulfapyridine. These observers were also able to show that *Cl. septicum* antitoxin and antibacterial serum and *Cl. welchii* antitoxin given intravenously were superior to sulfapyridine given by mouth. In intradermal injection with *Cl. septicum* the combined action of sulfapyridine and antitoxin or of sulfapyridine and antibacterial serum was shown under the conditions of their experiment to be more effective than any one of the agents alone. Morales-Otero and Gonzalez<sup>9</sup> reported that they were unable to protect mice from 1 minimal lethal dose of *Cl. welchii* by simultaneous intramuscular injection of azosulfamide.

Penicillin as a chemotherapeutic agent in the treatment of experimental gas gangrene infections was reported on by a group of British observers<sup>10</sup> in 1940. These workers injected *Cl. septicum* spore suspensions intramuscularly into mice, and when subcutaneous therapy was begun one hour after injection and large doses of penicillin were repeated for several days, excellent results were obtained.

Singer<sup>11</sup> studied the effect of the oral administration of certain sulfonamide compounds (sulfanilamide, sulfapyridine, dimethyldisulfanilamide and soluseptasine [disodium *p*-( $\gamma$ -phenylpropylamino)-benzenesulfonamido- $\alpha$ - $\gamma$ -disulfonate]) on mice inoculated subcutaneously with *Cl. welchii*, *Cl. septicum* and *Cl. novyi*. When 1 minimal lethal dose of *Cl. welchii* was used, good results were obtained. However, when multiples of 1 minimal lethal dose were used, some mice survived, but

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8. Henderson, D. W., and Gorer, P. A.: The Treatment of Certain Experimental Anaerobic Infections with Sulphapyridine and Immune Sera and the Problem of Synergistic Action, *J. Hyg.* **40**:345-364 (May) 1940.

9. Morales-Otero, P., and Gonzalez, L. M.: Effect of Azosulfamide (Neoprontosil) in Experimental Welchii Infections in Mice, *Proc. Soc. Exper. Biol. & Med.* **44**:532-534 (June) 1940.

10. Chain, E.; Jennings, M. A.; Florey, H. W.; Orr-Ewing, J.; Gardner, A. D., Sanders, A. G., and Heatley, N. G.: Penicillin as a Chemotherapeutic Agent, *Lancet* **2**:226-228 (Aug. 24) 1940.

11. Singer, E.: A Note on the Treatment of Gas Gangrene with Sulfanilamide and Related Compounds, *M. J. Australia* **1**:796-799 (June 8) 1940.

the majority were not saved. In *Cl. septicum* infections protection was obtained only with sulfapyridine, and in infections with *Cl. novyi* complete failure was encountered. In a subsequent paper Singer<sup>12</sup> reported that by using small amounts of antitoxic serum in *Cl. welchii* and *Cl. septicum* infections he was able to reduce the dose of sulfanilamide or of its derivatives needed to protect the mice.

In 1941 Longacre and Honold<sup>13</sup> reported studies in which they injected *Cl. welchii* intramuscularly in guinea pigs and administered sulfanilamide and derivatives of it intraperitoneally. They found that sulfanilamide and sulfapyridine were of little benefit and in no way modified the course of the infection. Although in animals treated with sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-4-methyl-thiazole) and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) gas gangrene developed and death followed, the infection was delayed and in many instances was less extensive.

Producing *Cl. welchii* infections in pigeons, Erb and Hodes<sup>14</sup> studied the relative therapeutic value of sulfanilamide, specific serum and radiation. Their results indicated that in the pigeon sulfanilamide and roentgen radiation were valueless. Serum alone proved beneficial.

McIntosh and Selbie<sup>15</sup> carried out studies using *Cl. welchii*, *Cl. septicum* and *Cl. novyi* for the organisms and sulfanilamide, sulfapyridine and sulfathiazole for the treatment. Mice were given intramuscular injections, and the organisms and the agents were administered simultaneously. The results were expressed in terms of the average number of days that the animals survived rather than on a basis of whether or not the animals lived or died, and unfortunately mortality beyond a three day period was not recorded in the report. On the whole, with local therapy all three drugs were of value in delaying death. Against *Cl. welchii* the three agents were of value in essentially equal degree. Against *Cl. septicum* sulfathiazole was strikingly superior; little effect was noted with the other agents. Against *Cl. novyi* good results were obtained with sulfathiazole, which again was superior to the other

12. Singer, E.: Experimental Studies on the Combined Sulphanilamide and Serum Treatment of Gas Gangrene Infections, *M. J. Australia* **2**:275-279 (Sept. 28) 1940.

13. Longacre, A. B., and Honold, E.: Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfamethyl-Thiazole in Experimental Gas Gangrene in Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* **46**:9-14 (Jan.) 1941.

14. Erb, W. H., and Hodes, P. J.: Therapeutic Results of Various Forms of Treatment in Experimentally Produced Gas Gangrene, to be published; cited by Fendergrass, E. P., and Hodes, P. J.: Roentgen Irradiation in Treatment of Inflammations, *Am. J. Roentgenol.* **45**:74-106 (Jan.) 1941.

15. McIntosh, J., and Selbie, F. R.: Chemotherapy of Gas Gangrene, *Lancet* **1**:240-242 (Feb. 22) 1941.



agents. Oral administration of the drugs resulted in almost complete failure, and the combined oral and local route offered no more than the local route alone.

A comparison of the effectiveness of sulfanilamide, sulfapyridine and paranitrobenzenesulfonamide with serum was made by Gordon and McLeod.<sup>16</sup> Mice and guinea pigs were inoculated subcutaneously with *Cl. welchii*, *Cl. septicum* and *Cl. novyi*. Serum when administered locally prior to the injection of the organisms was 100 per cent effective in preventing death of the animals from gas gangrene due to each of the three organisms. Under the same conditions the same degree of effectiveness was attained against *Cl. welchii* with sulfapyridine. However, this drug showed limited effectiveness against *Cl. septicum*. Sulfanilamide likewise showed some value against *Cl. welchii* but failed to protect against the other two organisms. Paranitrobenzenesulfonamide was of practically no value. None of the agents were effective when administered locally four and seven hours after inoculation with the organisms.

In 1941 Ozorio de Almeida and Pacheco<sup>17</sup> reported that favorable results were obtained when guinea pigs given subcutaneous injections of cultures of *Cl. septicum* were placed two hours after injection in an oxygen chamber. Pressure as high as 5 atmospheres of oxygen (3,800 mm. of mercury) was maintained, and the best results were obtained when the animals were kept in the chamber for repeated periods of one hour. These workers were not able to extend their favorable results to infections with *Cl. welchii* and *Cl. novyi*, nor were they able to obtain any therapeutic effect when solutions of sodium perborate were injected locally, intraperitoneally or intravenously.

Armstrong and Rae<sup>18</sup> produced gas gangrene by injecting washed cultures of *Cl. welchii* suspended in calcium chloride solution into the muscles of guinea pigs. One hour later they injected sulfanilamide, sulfapyridine, sulfathiazole and *P*-tolylamidine hydrochloride into the original site of injection. This method saved a high percentage of animals. Oral administration was found to be ineffective.

Bliss, Long and Smith,<sup>19</sup> using mice and inoculating cultures of *Cl. welchii* and suspensions of spores of *Cl. novyi* and *Cl. septicum*

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16. Gordon, J., and McLeod, J. W.: Relative Value of Sulfonamides and Antisera in Experimental Gas Gangrene, *Lancet* 1:407-409 (March 29) 1941.

17. Ozorio de Almeida, A., and Pacheco, G.: Ensaios de tratamento das Gangrenas gazosas experimentais pelo oxigenio em altas pressoes e pelo oxigenio em estado nascente, *Rev. brasil. de biol.* 1:1-10 (April) 1941.

18. Armstrong, A. R., and Rae, M. V.: Chemotherapy and Experimental Gas Gangrene, *Canad. M. A. J.* 45:116-118 (Aug.) 1941.

19. Bliss, E. A.; Long, P. H., and Smith, D. G.: Chemotherapy in Experimental Gas Gangrene and Tetanus Infection in Mice, *War Med.* 1:799-810 (Nov.) 1941.

intramuscularly simultaneously with various chemotherapeutic agents (sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine [2-(paraaminobenzenesulfonamido)-pyrimidine], sulfaguanidine [sulfanilylguanidine] and zinc peroxide), obtained favorable results with some of the drugs. Sulfadiazine was the most effective agent against *Cl. welchii* and *Cl. septicum*. Sulfathiazole was second best against the former and zinc peroxide against the latter. Contrary to their earlier report of success with sulfanilamide following intraperitoneal injection of *Cl. welchii* already noted, these authors found sulfanilamide to be valueless against intramuscular inoculation. It was also ineffective against *Cl. septicum*. Sulfaguanidine also was ineffective against these two organisms. Sulfapyridine was of some value against *Cl. septicum* but of no value against *Cl. welchii*. In the treatment of the animals inoculated with *Cl. novyi* the sulfonamide compounds used were valueless; on the other hand, zinc peroxide was effective in preventing death. The oral use of even the better agents was found to be inferior to local administration.

Sewell, Dowdy and Vincent<sup>20</sup> produced experimental gas gangrene in dogs by means of intramuscular injections of *Cl. welchii*. The therapeutic effects of roentgen radiation, sulfadiazine and a combination of the two were compared. The prophylactic effects of sulfadiazine, sulfanilamide and butyrylsulfanilamide were likewise studied. For prophylactic purposes the drugs were administered so that the blood concentration was raised to therapeutic levels prior to inoculation of the organisms. Sulfadiazine thus used protected 88 per cent of the animals, compared with a 16 per cent recovery rate for the controls. Sulfanilamide and butyrylsulfanilamide were definitely inferior to sulfadiazine. When chemotherapy was started after the infection was established, sulfadiazine protected only 28 per cent, compared with a 6.7 per cent recovery among the controls. Sulfadiazine was found to be superior to roentgen radiation alone and to roentgen radiation plus sulfadiazine. Of the animals receiving roentgen radiation therapeutically 26 per cent survived, compared with 17.9 per cent survival among the controls. The difference is not statistically significant.

It is to be noted that in all of the experiments referred to thus far the organisms were introduced by needle injection. What appears to us a well founded criticism of this method will be offered in a subsequent section.

The first experiments in which *Clostridium*-contaminated wounds were produced and treated with sulfonamide compounds applied locally were those reported by Legroux<sup>21</sup> in 1940. He attempted to reproduce

20. Sewell, R. L.; Dowdy, A. H., and Vincent, J. G.: Chemotherapy and Roentgen Radiation in *Clostridium Welchii* Infections, *Surg., Gynec. & Obst.* **74**:361-367 (Feb. 16) 1942.

21. Legroux, R.: Chimio-prévention de l'infection bactérienne des plaies de guerre, *Mém. Acad. de chir.* **66**:415-424 (April 17-24) 1941.

war wounds in guinea pigs. He made thigh wounds, traumatized the muscle and produced contamination by adding a piece of cloth soaked with *Cl. welchii* or *Cl. histolyticum*. Sulfanilamide was dusted into the wounds at the time of contamination, and then the wounds were sutured. Animals thus treated lived from four to seven days, whereas the controls died within three days. If at the end of three days the wounds were reopened and more sulfanilamide was applied, the animals survived. Legroux found that if the drug was administered later than one hour after contamination treatment was ineffective. Likewise, oral administration of the drug was of no value.

Caldwell<sup>22</sup> produced traumatic wounds and compound fractures in guinea pigs, contaminated them with *Cl. welchii* and compared the effects of local and intraperitoneal administration of sulfanilamide, local application of zinc peroxide and roentgen therapy. In the wounds treated with sulfanilamide therapy was delayed one to six hours and was combined with debridement, after which the wounds were sutured. The results were poor; only 4 of 19 animals survived. Sulfanilamide administered intraperitoneally every six hours and combined with debridement and irrigation of the wounds two hours after contamination resulted in the survival of 7 of 9 animals. In another experiment debridement and irrigation and application of zinc peroxide were done two hours after contamination. The wounds were closed with suture material. Of 5 animals 4 survived. Roentgen radiation saved only 3 of 7 animals, but these results cannot be compared with those of the experiments with sulfanilamide and zinc peroxide since no debridement or irrigation was carried out.

Using a technic similar to that of Legroux, Hawking<sup>23</sup> carried out thorough studies on experimental gas gangrene in guinea pigs. He found that the application of sulfonamide compounds to the wounds at the same time as the insertion of the organisms saved a large proportion of the animals infected with *Cl. welchii* and with *Cl. septicum* but had slight influence on infections with *Cl. novyi*. Sulfanilamide was superior to sulfapyridine in preventing infection with *Cl. welchii*, but it had practically no activity against *Cl. septicum*. Sulfathiazole was the most effective compound used. Hawking compared the effect of delaying local treatment with sulfathiazole in 4 of his experiments with *Cl. welchii* and in one with *Cl. septicum*. Although the individual results were not indicated, he stated that taking the series as a whole he found that when treatment was immediate 67 per cent of the animals survived,

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22. Caldwell, G. A.: Treatment of Gas Gangrene Experimentally Produced, *J. Bone & Joint Surg.* **23**:81-85 (Jan.) 1941.

23. Hawking, F.: Prevention of Gas Gangrene Infections in Experimental Wounds by the Local Application of Sulphonamide Compounds and by Sera, *Brit. M. J.* **1**:263-268 (Feb. 22) 1941.

that when treatment was delayed two hours 26 per cent survived and that when treatment was delayed six hours none of the animals survived. Local application of sulfathiazole to the wound was more effective in preventing death than intraperitoneal administration. Hawking also observed that the development of the infection in these wounds could be prevented by prophylactic administration of antitoxic serum. Monovalent serums specific for *Cl. welchii*, *Cl. septicum* or *Cl. novyi* protected the animals against these organisms respectively. A commercial polyvalent serum gave protection against most strains of *Cl. welchii* and *Cl. novyi* but not against *Cl. septicum*. In those instances in which serum was effective it was superior to sulfathiazole. In a subsequent study<sup>24</sup> Hawking compared sulfathiazole with sulfaguanidine and sulfadiazine and concluded that sulfaguanidine was definitely inferior to sulfathiazole while sulfadiazine was no better and probably inferior.

Bonnin and Fenner,<sup>25</sup> working under trying conditions in an army camp in Australia, carried out some interesting experiments, attempting to simulate war wounds as closely as possible. Wounds were produced in the muscles of guinea pigs; bone was also fractured. Into this traumatized tissue sterile garden soil was rubbed, and organisms were inserted. Sulfanilamide was the only drug used, and 0.5 Gm. of this was placed into the wound before closure. Twelve hours later the animals were reoperated on; complete excision of the damaged tissue was carried out, and the wounds were closed after the insertion of 1 Gm. of sulfanilamide. The results with *Cl. welchii* were good; with *Cl. septicum*, so far as survival was concerned, the results were not good, but there was definite prolongation of life. No success was obtained in the series of animals inoculated with *Cl. novyi*.

Reed and Orr<sup>26</sup> in a preliminary paper published in 1941 and in a subsequent one more recently<sup>27</sup> reported carrying out a thorough study in which a great number of experimental animals were used. In addition to the three species of *Clostridium* tested by most observers, a fourth, *Clostridium sordellii*, as well as a mixture of these with *Clostridium sporogenes* and *Cl. histolyticum* was used. Wounds were produced in guinea pigs in essentially the same manner as in the experiments of Legroux and others<sup>28</sup> and were closed with sutures. The chemo-

24. Hawking, F.: Sulphadiazine and Sulphanil-Guanidine Against Gas Gangrene, *Brit. M. J.* 2:29-30 (July 5) 1941.

25. Bonnin, N. J., and Fenner, F.: Local Implantation of Sulphanilamide for Prevention and Treatment of Gas Gangrene in Heavily Contaminated Wounds: Suggested Treatment for War Wounds, *M. J. Australia* 1:134-140 (Feb. 1) 1941.

26. Reed, G. B., and Orr, J. H.: Chemotherapy in Experimental Gas Gangrene, *Lancet* 1:376-379 (March 22) 1941.

27. Reed, G. B., and Orr, J. H.: Local Chemotherapy of Experimental Gas Gangrene, *War Med.* 2:59-78 (Jan.) 1942.

28. Caldwell.<sup>22</sup> Hawking.<sup>23</sup> Bonnin and Fenner.<sup>25</sup>

therapeutic agents were applied locally, both immediately after inoculation and after stated intervals. Oral therapy as well as a combination of local and oral therapy was also used. These observers concluded that the wounds contaminated with *Cl. welchii* responded most readily to chemotherapy, that those contaminated with *Cl. septicum* and *Cl. novyi* responded less well and that those contaminated with *Cl. sordellii* were much more resistant. With reference to the group of causative organisms as a whole, sulfathiazole was the most effective agent, sulfadiazine next and then followed sulfamethylthiazole, sulfapyridine, sulfaguanidine and sulfanilamide. Delay in instituting therapy was found to reduce the beneficial action of the drugs. Local treatment was found to be superior to oral. In another group of experiments<sup>29</sup> the effectiveness of zinc peroxide was studied. When the drug was applied immediately to wounds contaminated with *Cl. welchii* and *Cl. novyi*, all of the animals were saved. On the other hand, only half of the animals with *Cl. septicum*-contaminated wounds survived. Likewise, 50 per cent survival was obtained against the vegetative form of *Cl. sordellii*, yet against the spore form of this organism the recovery rate was increased to 80 per cent. Thus the results with zinc peroxide applied immediately compare favorably with those recorded for sulfathiazole. Delay in instituting therapy caused marked reduction in effectiveness, and here zinc peroxide was somewhat less effective than sulfathiazole.

This study of the literature has left us in a confused state of mind, and undoubtedly the reader of this brief review has been similarly affected. Usually when there is diversity of opinion with regard to any treatment, either there is an obvious reason for the variation in results, or the treatment is given undeserved credit for results due to other factors. Are there any obvious reasons why there is diversity of opinion relative to the value of chemotherapy in experimental gas gangrene? We believe there are.

Undoubtedly one of the reasons for some of the differences rests in the method used to produce the experimental lesion. Some observers injected the organisms subcutaneously; some injected them intramuscularly, while still others produced muscle wounds into which organisms were placed before closure. In some cases the needle injection of the bacteria was accompanied by muscle trauma, while in others no such trauma was introduced. Some authors reported adding to the organisms calcium chloride, and there were instances in which no lesion was produced in the absence of this chemical. Varying results can obviously be explained on the basis of differences in source as well as differences in virulence among the strains of organism used. With spore-producing

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29. Reed, G. B., and Orr, J. H.: Treatment of Experimental Gas Gangrene with Zinc Peroxide, *War Med.* 2:79-82 (Jan.) 1942.

and toxin-producing bacteria, such as the Clostridia, one has the choice of introducing either spores or vegetative forms with or without preformed toxin, and indeed all of these methods were used. That chemotherapy gives differing results with spores as against vegetative forms is borne out by some of the observations of Reed and Orr. The type of animal selected for experimentation and differences in dosages as well as in routes of administration are all additional reasons for variations in results which are sufficiently obvious to need no further elaboration.

On several important points there has been general agreement among the various reports. Most observers have expressed the opinion that chemotherapy is of some value in preventing experimental gas gangrene. Those who have compared serum with chemotherapy have stated that the former is more effective but that they have been impressed with the superiority of the combination over either alone. That local application of the chemotherapeutic agents is better than oral or parenteral administration has been accepted. Likewise the consensus is that *Cl. novyi* infections are refractory to the sulfonamide compounds. The only two observers who have used zinc peroxide against this organism have reported excellent results. Those who have worked with experimental roentgen radiation have been unanimous as to its lack of value. Just which of the sulfonamide compounds is best is unsettled. Most experiments have indicated that sulfadiazine and sulfathiazole are superior to the other sulfanilamide derivatives. In a later section some of the discrepancies as well as points of agreement will be pointed out in detail, and comparisons will be made with our own results.

#### EXPERIMENTAL PROCEDURES

In the experiments which are to be described in detail, wounds were produced in anesthetized guinea pigs and contaminated with certain of the Clostridia associated with gas gangrene in human beings. Subsequently these wounds were treated locally with certain of the newer chemotherapeutic agents for the purpose of evaluating the effectiveness of these agents in the prevention of experimental gas gangrene.

*Cl. welchii* (*Clostridium perfringens*), *Cl. septicum* (*vibrio septique*), *Cl. novyi* (*Clostridium oedematiens*) and *Cl. sordellii* (*Clostridium oedematoides*) were the organisms used. The first three are the Clostridia most commonly associated with clinical gas gangrene. The fourth, although not encountered as frequently as the other three, has also been reported as the causal agent of disease in human beings.<sup>30</sup> Two strains of *Cl. welchii* were used. The source of the strain used in experiment 1 is not clear; however, among several strains tested it proved to be the most pathogenic for guinea pigs. The strain used in experiment 2 had been isolated from a case of gas gangrene.<sup>31</sup> The other Clostridia were stock strains kept on hand in our own laboratory.

30. Humphreys, F. B.: *Anaerobic Bacteria: The "Gas Gangrene" Group*, in Gay, F. P., and others: *Agents of Disease and Host Resistance*, Springfield, Ill., Charles C. Thomas, Publisher, 1935, chap. 38.

31. This was furnished by Dr. F. B. Humphreys, of the Department of Bacteriology, Columbia University College of Physicians and Surgeons.

Cultures were grown in dextrose (0.2 per cent) cooked beef heart mediums for eighteen hours. (Four hour cultures were used in some wounds in experiment 3, and twenty-four hour cultures were used in experiment 4.) Cultures were tested for contamination by frequent platings. Titration of many of the cultures was carried out in order to estimate the number of organisms in each inoculum. The eighteen hour cultures of *Cl. welchii* contained not less than  $10^9$  organisms per cubic centimeter; those of *Cl. septicum*, not less than  $10^6$  organisms per cubic centimeter; and those of *Cl. novyi*, not less than  $10^8$  organisms per cubic centimeter. The four hour cultures on the whole contained correspondingly fewer organisms.

Experiments were carried out on 528 guinea pigs. Animals weighing from 250 to 300 Gm. (with an occasional larger or smaller one) were used. Throughout the period of postoperative observation the animals were kept separately in adequately-sized cages and were fed a diet consisting of oats and fresh green vegetables. On the whole they remained free from intercurrent infections.

The anesthetic agent (except for a few animals in experiment 3 on which open drop ether was used) was soluble pentobarbital. This was administered subcutaneously in the form of a 1 per cent solution in sterile distilled water. Four cubic centimeters of this solution per kilogram of body weight of the animal produced satisfactory anesthesia and lasted approximately four hours. Thus additional anesthesia was not required in those animals operated on a second time or treated following the first operation.

All of the wounds were produced in the posterior buttock (gluteal) region. This area was selected for the following reasons: 1. It provided a muscular region in which a soft tissue wound of the desired size could be readily produced. 2. It was a relatively immobile muscular area. 3. Dressings could be arranged over the wounds so that the animal could not disturb them. The hair over the area selected was clipped, and the skin was prepared with tincture of iodine. Sterile technic was used throughout. A standard type of dressing was adopted for initial as well as for subsequent dressings. This consisted of a small square of petrolatum gauze placed immediately over the wound and held in place by adhesive tape.

The chemotherapeutic agents<sup>32</sup> used in this study were as follows: sulfanilamide, sulfadiazine, sulfathiazole, sodium sulfadiazine, sodium sulfathiazole, gramicidin and zinc peroxide. The sulfonamide compounds were introduced directly into the wound in the dry state; zinc peroxide was used as a creamy suspension (the accepted method of clinical use), and gramicidin was applied as an alcoholic extract on saturated cotton so that it would remain in the wound. In each instance the quantity of drug used was based on the amount necessary to fill the wound and to maintain contact with all parts of it.

After each experiment the animals were carefully observed at frequent intervals. Those that died were submitted to autopsy. The pathologic appearance of the lesion produced by each species is characteristic and is described in another section. In many instances cultures were taken from the edema fluid and exudate and from the heart's blood. In almost every case these yielded growth of the organism used. Twenty-eight of the animals died from causes other than gas gangrene, such as pneumonia or gastroenteritis. Those dying without evidence of gas gangrene but living beyond the period during which gas gangrene would

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32. Dr. René Dubos of the Rockefeller Institute provided the gramicidin; E. I. DuPont de Nemours and Company (Inc.) contributed the zinc peroxide, and Lederle Laboratories, Inc., supplied the other drugs used in this study.

have been expected to develop are for the purpose of this study classified as survivals.

*Experiment 1.*—An incision 0.5 cm. long was carried through the skin and the subcutaneous tissue down to the muscle, which was incised transversely. The resulting muscle incision was approximately 0.5 cm. wide and 0.5 cm. deep. The tissue on both margins of the incised muscle wound was crushed with a small hemostat. One-tenth cubic centimeter of an eighteen hour culture of *Cl. welchii* was placed into the wound. Dressing was applied. After two hours one group of

TABLE 1.—*Results of Local Chemotherapy in Experimental Wounds Contaminated with Cl. Welchii*

	Total	Deaths	Recoveries	Survival Rate (Per Cent)
Controls .....	20	14	6	30
Debridement and irrigation only.....	10	8	2	20
Sulfanilamide .....	10	4	6	60
Sulfanilamide plus debridement and irrigation	10	0	10	100
Sulfadiazine .....	10	3	7	70
Sulfadiazine plus debridement and irrigation	10	3	7	70
Sodium sulfadiazine .....	10	2	8	80
Sodium sulfadiazine plus debridement and irrigation .....	10	2	8	80
Sulfathiazole .....	10	3	7	70
Sulfathiazole plus debridement and irri- gation .....	10	2	8	80
Sodium sulfathiazole .....	10	2	8	80
Sodium sulfathiazole plus debridement and irrigation .....	10	0	10	100
Zinc peroxide .....	10	8	2	20
Zinc peroxide plus debridement and irri- gation .....	10	4	6	60

TABLE 2.—*Summary of Recovery Rates After Local Chemotherapy in Wounds Contaminated with Cl. Welchii*

	Recovery Rates (Per Cent)
Controls .	30
Debridement and irrigation.....	20
Chemotherapy alone .....	63
Chemotherapy plus debridement and irrigation	82

these animals was reoperated on. The skin incision was prolonged to double its original length, and all of the traumatized muscle was excised. Great care was taken not to open any new tissue planes and subject them to contamination. The wound was irrigated with 20 to 30 cc. of physiologic solution of sodium chloride and filled with one of the chemotherapeutic agents. In another group of animals debridement and irrigation were carried out, but no chemotherapeutic agent was applied to the wound. In still another group debridement and irrigation were not performed, but the chemotherapeutic agents were applied. Animals which received only initial wounding and contamination were used for controls. The amount of drug applied in each instance was 100 mg. except for sodium sulfathiazole, of which 150 mg. was necessary to fill the wound. The results of this experiment are recorded in table 1.



*Experiment 2.*—An incision 2 cm. long was carried through the skin and the subcutaneous tissue, and the underlying muscle was exposed. A block of muscle measuring on an average 1.5 by 1.5 by 0.5 cm. and having an average weight of 400 mg. was excised. In making this wound an effort was made to produce considerable trauma. Into each wound a small piece of sterile cotton was placed,

TABLE 3.—*Results of Local Chemotherapy in Experimental Wounds Contaminated with Cl. Septicum*

	Total	Deaths	Recoveries	Survival Rate (Per Cent)
Controls.....	37	28	9	24
Sulfanilamide.....	15	1	14	93
Sulfadiazine.....	15	5	10	67
Sodium sulfadiazine.....	17	2	15	88
Sulfathiazole.....	15	0	15	100
Sodium sulfathiazole.....	15	1	14	93
Zinc peroxide.....	15	8	7	47

TABLE 4.—*Results of Local Chemotherapy in Experimental Wounds Contaminated with Cl. Novyi*

	Total	Deaths	Recoveries	Survival Rate (Per Cent)
Controls.....	27	26	1	3.7
Sulfanilamide.....	10	10	0	0.0
Sulfadiazine.....	10	10	0	0.0
Sodium sulfadiazine.....	20	19	1	5.0
Sulfathiazole.....	10	10	0	0.0
Sodium sulfathiazole.....	20	16	4	20.0
Zinc peroxide.....	19	14	5	26.0

TABLE 5.—*Results of Local Chemotherapy in Experimental Wounds Contaminated with Cl. Sordellii*

	Total	Deaths	Recoveries	Survival Rate (Per Cent)	Average Hours of Life
Controls.....	5	5	0	0	26
Sulfanilamide.....	5	5	0	0	34
Sulfadiazine.....	5	4	1	25	40
Sodium sulfadiazine.....	5	5	0	0	63
Sulfathiazole.....	5	4	1	25	61
Sodium sulfathiazole.....	5	5	0	0	81
Zinc peroxide.....	5	5	0	0	35

underneath which 0.5 cc. of an eighteen hour culture of *Cl. septicum*, *Cl. novyi* or *Cl. sordellii* was flooded. A dressing was applied.

Two hours after contamination the dressing and the saturated cotton were removed from one group of animals and a chemotherapeutic agent was placed in the wound. Neither irrigation nor debridement was carried out. The amounts of drugs used varied slightly since the object was to fill each wound and to bring the agent into contact with all parts. On an average 250 mg. of sulfadiazine or 500 mg. of the other agents was placed in each wound. The other group of animals received no treatment and was used as a control. The results of this experiment are recorded in tables 3, 4 and 5.

*Experiment 3.*—The operative technic and the method of contamination in this experiment were the same as for experiment 2. The manner of treatment differed in that one and one-half hours after contamination debridement of the wound followed by irrigation with physiologic solution of sodium chloride was carried out. Next 100 to 200 mg. of each chemotherapeutic agent was used, except for gramicidin, 0.5 cc. of which was placed into the wound on cotton. Three groups

TABLE 6.—*Results of Local Chemotherapy in Experimental Wounds Contaminated with Cl. Welchii*

	Total	Deaths	Recoveries	Survival Rate (Per Cent)
Controls.....	5	3	2	40
Saline irrigation.....	5	4	1	20
Alcohol.....	5	4	1	20
Sulfanilamide.....	4	1	3	75
Zinc peroxide.....	5	2	3	60
Gramicidin.....	5	1	4	80

TABLE 7.—*Results of Local Chemotherapy in Experimental Wounds Contaminated with Cl. Septicum*

	Total	Deaths	Recoveries	Survival Rate (Per Cent)
Controls.....	5	5	0	0
Saline irrigation.....	5	5	0	0
Alcohol.....	5	3	2	40
Sulfanilamide.....	5	3	2	40
Zinc peroxide.....	5	4	1	20
Gramicidin.....	5	3	2	40

TABLE 8.—*Results of Local Chemotherapy in Experimental Wounds Contaminated with Cl. Novyi*

	Total	Deaths	Recoveries	Survival Rate (Per Cent)
Controls.....	3	3	0	0
Saline irrigation.....	3	3	0	0
Alcohol.....	3	2	1	33
Sulfanilamide.....	3	2	1	33
Zinc peroxide.....	3	2	1	33
Gramicidin.....	3	3	0	0

of animals served as controls. One group received no treatment; another received debridement and irrigation only, and the third received 0.5 cc. of 95 per cent alcohol. The last-named group served as a control for the gramicidin-treated animals inasmuch as this agent was administered in the form of an alcoholic extract. The results of this experiment are recorded in tables 6, 7 and 8.

*Experiment 4.*—The operative technic in this experiment was somewhat similar to that used in experiment 2. The same type of incision was used, and the same-

sized block of muscle was exposed. However, instead of the muscle being excised, it was thoroughly crushed with a hemostat. A small piece of cotton was inserted into the wound, and 0.5 cc. of a twenty-four hour culture of *Cl. sordellii* was flooded into the wound. At the end of two hours the traumatized muscle was excised; the wound was irrigated with physiologic solution of sodium chloride, and the chemotherapeutic agents in amounts used in experiment 2 were applied. One group of animals received debridement and irrigation only, and a third group received no treatment and was used as a control. The results of these experiments are recorded in table 9.

#### RESULTS OF EXPERIMENTS

The results of experiments 1, 2, 3 and 4 are presented in tables 1 to 10. To determine the significance of the difference between the various survival rates which appear in these tables the statistical method has been used. The value of such an analysis in estimating the significance of experimental data is self evident.

TABLE 9.—*Results of Local Chemotherapy in Experimental Wounds Contaminated with Cl. Sordellii*

	Total	Deaths	Recoveries	Survival Rate (Per Cent)	Average Hours of Life
Controls .....	3	3	0	0	35
Debridement and irrigation only	3	3	0	0	34
Sulfadiazine .....	3	3	0	0	59
Sodium sulfadiazine .....	3	3	0	0	68
Sulfathiazole .....	3	3	0	0	75
Sodium sulfathiazole .....	3	3	0	0	84
Zinc peroxide .....	3	3	0	0	40

Study of table 1, in which the results obtained with *Cl. welchii* are recorded, reveals that sulfadiazine, sulfathiazole and their sodium salts (used with or without debridement and irrigation) and sulfanilamide (used with debridement and irrigation) each increases the survival rate when compared with that for the control animals to a figure which has statistical significance. The survival rate for the animals treated with sulfanilamide without debridement and irrigation and with zinc peroxide plus debridement and irrigation when compared with the survival rate for the controls is not of statistical significance. It will be noted in table 2 that chemotherapy combined with debridement and irrigation is superior to chemotherapy used alone. This observation is in conformity with well accepted principles of surgery. On the other hand, we are at a loss for an explanation of the fact that there is no difference (the difference between 30 and 20 per cent in this instance is not of statistical significance) between the survival rates for the controls and for the animals treated by debridement and irrigation.

From a study of table 3, in which the results with *Cl. septicum* are recorded, we find that the difference between the survival rates for animals treated with each of the sulfonamide compounds used (sulfanilamide, sulfadiazine, sulfathiazole, sodium sulfadiazine and sodium sulfathiazole) considered individually and the controls is of statistical significance. The difference between the survival rate for the zinc peroxide-treated group of animals and the control group is not of statistical significance. The conclusion to be drawn here is that in the prevention of gas gangrene in *Cl. septicum*-contaminated wounds the aforementioned sulfonamide compounds are of definite value while zinc peroxide is of uncertain value.

Table 4 records the results of experiments with *Cl. novyi* and reveals that except for sodium sulfathiazole the sulfonamide compounds used were of little or no value in preventing death from gas gangrene due to

TABLE 10.—*Average Survival Time After Local Chemotherapy in Experimental Wounds Contaminated with Cl. Sordellii*

	Average Survival Time (Hr.)
Control .....	29.5
Debridement and irrigation only.....	34.0
Sulfanilamide .....	33.0
Zinc peroxide .....	39.6
Sulfadiazine .....	48.0
Sulfathiazole .....	67.0
Sodium sulfadiazine .....	68.0
Sodium sulfathiazole .....	82.0

this organism. The difference between the survival rate for the sodium sulfathiazole-treated animals and that for the controls is not of statistical significance. However, the survival rate obtained among the zinc peroxide-treated animals, viz. 26 per cent, is significant. From this we conclude that zinc peroxide has definite value in preventing the development of gas gangrene in *Cl. novyi*-contaminated wounds.

Tables 5 and 9 show the results of the experiments with *Cl. sordellii*. It is obvious from these tables that chemotherapy used after a two hour interval is of no value in preventing death from experimental gas gangrene due to this organism. When one considers these two tables together and calculates in hours the average time of survival for the animals, the results shown in table 10 are obtained.

It is apparent from table 10 that by using sulfathiazole, sulfadiazine or their sodium salts the average duration of life of the animals can be doubled when compared with that of the controls and that while these chemotherapeutic agents do not prevent gas gangrene in *Cl. sordellii*-contaminated experimental wounds they do retard its development.

Tables 6, 7 and 8 record the results of additional experiments with *Cl. welchii*, *Cl. septicum* and *Cl. novyi*. The only information added as the result of these experiments is that the use of an alcoholic extract of gramicidin is of value in preventing gas gangrene in *Cl. welchii*-contaminated wounds. This agent is of little or no value against the two other organisms. These are interesting observations, but until further experiments with gramicidin are performed, their importance should not be overemphasized.

The lesions produced in guinea pigs by each species of *Clostridium* under the conditions of these experiments presented certain characteristics which are worthy of note.

*Cl. Welchii*.—Animals infected with *Cl. welchii* showed in the first twenty-four to forty-eight hours following contamination extensive edema, discoloration and crepitation involving the thigh and spreading along the subcutaneous tissues of the abdomen and the thorax. Surprisingly, in some instances infections as extensive as this subsided spontaneously. Occasionally animals died before the disease progressed to such a point. Those living longer than forty-eight to seventy-two hours almost always showed necrosis around the wound and in the thigh and occasionally on the abdominal wall. A number of these lesions healed, and the animals ultimately recovered. Among the *Cl. welchii*-infected animals that died there was a rather typical picture. Around the wound (and here the extent seemed to depend on how long the animal had survived the infection), the muscle was pale and necrotic. Beyond this area there was congestion of the muscles, gas and hemorrhagic exudate in the tissue planes. The spread of the exudate was most rapid along the subcutaneous tissue planes. The exudate was usually serosanguineous but occasionally was slightly gelatinous. This fluid consistently yielded *Cl. welchii* on culture, and frequently the organism could be grown from the blood stream. The mortality rate in all experiments for all untreated control animals of the *Cl. welchii* group was 73 per cent, and the average duration of life for those controls that died was fifty hours from the time of contamination.

Many of the features of the *Cl. welchii* infection were observed in gas gangrene due to *Cl. septicum*, *Cl. novyi* and *Cl. sordellii*, particularly the mode of spread and the presence of the organisms in exudate and heart's blood. There were, however, certain features which made it possible to distinguish these lesions from one another.

*Cl. Septicum*.—The mortality rate among all the *Cl. septicum*-contaminated controls was 80 per cent, and the average duration of life was nineteen hours. Animals with *Cl. septicum* infections died before showing as extensive clinical disease as did those infected with the other species; the process once initiated was rapid. At autopsy the chief distinguishing characteristic of *Cl. septicum* infection was the brilliant

red color of the muscle involved. The exudate and other features presented a picture not unlike that of infections with *Cl. welchii* save for the fact that little or no necrosis was evident.

*Cl. Novyi*.—The animals infected with *Cl. novyi* were characterized by the extensive edema of the thigh and the abdominal wall. In many instances this extended to the level of the axillas. At autopsy there was usually a limited zone of necrosis at the site of the original muscle wound and hemorrhage, exudate and gas in the tissues immediately surrounding. Muscle was usually congested but not so brilliantly as in *Cl. septicum* infections. The exudate in the subcutaneous tissues of the abdominal wall and the thorax was thick and gelatinous and almost colorless. The mortality rate among all of the untreated controls was 97 per cent, and the average duration of life was seventy hours.

*Cl. Sordellii*.—Infections due to *Cl. sordellii* were not unlike those caused by *Cl. novyi* save for the fact that the colorless gelatinous edema was thicker and more extensive. None of the control animals in this group survived, and the average duration of life of the control animals after contamination was twenty-nine hours.

#### COMMENT

Infection in the experiments carried out by many observers was produced by subcutaneous, intramuscular or intraperitoneal needle injection of the organisms. These methods, while they afford a satisfactory and consistent mode of producing gas gangrene in laboratory animals, differ so greatly from the manner in which contamination or infection takes place in traumatic wounds in human beings that the results cannot be accurately compared with the conditions which actually prevail in fresh traumatic wounds in human beings.

In studying this problem it has seemed to us that nothing less than a true to life method of effecting trauma, contamination and prophylaxis or treatment in experimental animals should be employed to draw comparisons with gas gangrene in human beings. A wound reproducing accurately all true to life factors and eliminating all artificial elements cannot be produced in experimental animals under laboratory conditions. Our purpose has been, therefore, to simulate as closely as possible contaminated traumatic wounds in human beings, at the same time endeavoring to keep such wounds simple in order to avoid the introduction of extraneous factors.

For this reason the use of such foreign bodies as metal or soil embedded in the tissues was decided against. We did, however, in some experiments place a small piece of cotton superficially in the wound in order to retain the inoculum and prevent its spilling from the wound.

This simulated foreign bodies such as clothing. Bone trauma (i. e. experimental compound fracture) was not studied because of its great variation.

Once the wounds were produced and contaminated, the question was raised whether to close these wounds with suture material or to leave them open. It was decided to leave them open on the basis of greater simplicity and the closer similarity to human lesions. While we feel that a muscle wound produced, contaminated and left without closing with suture material constitutes a more nearly true to life situation than does any type of wound heretofore suggested, we in no sense believe that our method is the final answer to the problem of producing the experimental lesion. The fact that with Cl. welchii and Cl. septicum 27 and 20 per cent respectively of the untreated control animals survived is sufficient to suggest that improvement in our method needs to be sought. It is entirely possible that some of the wounds failed to offer adequate anaerobic conditions and that hence a certain percentage of control animals survived. In this connection it is interesting to note the observation of Reed and Orr that if the wounds were left open or if they subsequently opened as a result of incomplete or faulty closure, infections failed to develop in a fair number of animals, or transient infections developed from which the animals recovered without treatment. Using a wound closed with sutures, both Reed and Orr and Hawking were able to obtain a higher mortality rate among their control animals than we were, using a contaminated but unsutured wound.

We believe that in order to obtain true to life conditions of prophylaxis an interval must lapse between contamination of the experimentally produced wound and the introduction of the chemotherapeutic agent, a factor which some workers have not taken into consideration. Two hours was decided on as a desirable interval. Possible objection might be raised to the shortness of this period when compared with the time which lapses between injury and treatment of human patients, particularly in wartime. It must be pointed out that two hours seems to us a fair interval on the basis of the facts that in small untreated laboratory animals gas gangrene is a rapidly progressive disease and that the interval between contamination and death is but a fraction of the time which usually intervenes in human patients. There should be further studies in which varying periods are allowed to intervene between contamination and treatment.

Local application of the chemotherapeutic agent was the only method of treatment used. There is already at hand sufficient data to indicate that in experimental gas gangrene local application is more efficacious than oral or parenteral administration of the sulfonamide compounds. For zinc peroxide and gramicidin the local route is the only one feasible. The quantity of drug used was based on the amount necessary to fill

the wound and to make adequate contact with all parts of it rather than on the body weight of the animal. When the amount of sulfonamide compound placed in each wound is calculated on the basis of the body weight of the animal and comparison is made with the customary doses for human beings, it becomes apparent that a generous amount was used in each instance.

Only pure cultures of pathogenic *Clostridia* were used to produce gas gangrene in our experiments. It must be emphasized that in this respect experimental gas gangrene as produced in this study as well as in that of many other observers differs from clinical gas gangrene in human beings. Frequently in clinical cases other organisms, both aerobic and anaerobic, are isolated in addition to one or more of the pathogenic *Clostridia*, and in such instances the possibility of synergism should be kept in mind. Studies using mixtures of organisms as well as mixtures of chemotherapeutic agents are clearly indicated.

As has been pointed out previously, lack of uniformity in methods renders accurate correlation between observations of the various authors almost impossible. There are, however, several outstanding discrepancies as well as certain points of agreement which seem worth commenting on and comparing with our own results.

In regard to *Cl. welchii* infections treated with sulfanilamide, Hawking reports 72 per cent survivals, Reed and Orr, 40 per cent, Bonnin and Fenner, 80 per cent and Bliss, Long and Smith, complete failure. All of these observers administered drug and organisms simultaneously. In experiments in which an interval was allowed to lapse between contamination and therapy, we find our own result of 100 per cent, that of Caldwell of 21 per cent and that of Reed and Orr of 0 per cent. Sulfadiazine as used against *Cl. welchii* by Reed and Orr yielded 80 per cent survivals, and as used by us, 70 per cent survivals, compared with 43 per cent obtained by Hawking and 26 per cent obtained by Bliss, Long and Smith. With sulfathiazole Reed and Orr saved 97 per cent of their animals; we were able to save 75 per cent; Hawking saved 76 per cent, and Bliss, Long and Smith, 13 per cent.

One of the most outstanding discrepancies is that concerning the use of zinc peroxide against *Cl. welchii*. This agent in the experiments of Johnson and Meleney was found to be 94 per cent effective, whereas Bliss, Long and Smith using essentially the same technic found that only 1.7 per cent of their animals were saved. This is difficult to understand even when the fact is taken into consideration that guinea pigs were the experimental animals for one group of observers and mice for the other. When Reed and Orr allowed three hours to lapse between contamination and treatment, 60 per cent of their zinc peroxide-treated animals survived. This is comparable to our own result of 60 per cent under similar conditions.



With *Cl. septicum* as the organism and sulfanilamide as the drug, Bliss, Long and Smith, Bonnin and Fenner and Hawking encountered complete failure, while Reed and Orr had 25 per cent survivals as compared with our own survival rate of 100 per cent. Using sulfadiazine, Reed and Orr obtained 100 per cent recoveries and Bliss, Long and Smith, 98 per cent, as against our own of 67 per cent. With sulfathiazole, Reed and Orr reported 87 per cent survivals; Hawking, 75 per cent, and Bliss, Long and Smith, 58 per cent, while the results reported by us were 100 per cent survivals, even when a two hour period lapsed between contamination and treatment. It is particularly interesting to note that when Reed and Orr allowed a three hour and a six hour interval to intervene they also obtained 100 per cent survivals. With zinc peroxide against *Cl. septicum* there is similarity in the results of several observers. In those experiments in which the organisms and the chemotherapeutic agent were administered simultaneously, Reed and Orr obtained 50 per cent survivals, and Bliss, Long and Smith, 62 per cent. On the other hand, when Reed and Orr allowed an interval of three or six hours to intervene, 30 per cent of their animals survived. In our series 47 per cent survived.

Concerning the results with *Cl. novyi* there is more uniform agreement; yet even here discrepancies continue to appear. Using sulfanilamide against this organism Reed and Orr and Hawking had 24 and 28 per cent survivals respectively, whereas the experiments of Bliss, Long and Smith, Bonnin and Fenner and us showed no recoveries. Using sulfadiazine Reed and Orr obtained 40 per cent recoveries when the drug and the organisms were given simultaneously and 100 per cent when an interval was allowed. With this same drug and organism Bliss, Long and Smith obtained 4 per cent survivals, and we had none. Sulfathiazole gave even better results against *Cl. novyi* as used by Reed and Orr, who obtained 85 per cent survivals when the drug was administered at the same time as the organisms. When two and three hours intervened, the results were even better, viz. 100 per cent. Hawking obtained 33 per cent survivals; Bliss, Long and Smith, 6 per cent, and we again had none. Using zinc peroxide against *Cl. novyi* and administering the drug and the organisms simultaneously, Reed and Orr had 100 per cent survivals, and Bliss, Long and Smith, 98 per cent. When three hours lapsed between contamination and therapy, Reed and Orr encountered complete failure, but in experiments in which six hours lapsed they reported 40 per cent recoveries, giving a mean of 20 per cent, which is comparable to our own survival rate of 26 per cent.

In no sense are these comparisons to be considered as a complete report on all of the work done along these lines, nor are they even to be thought of as representing all of the observations made by any one observer. Certain findings, however, have been briefly reviewed from

which comparisons can be made. The recording of them serves to emphasize the need for a uniform method of study for this problem.

Because a clearcut and universally accepted decision has not been reached as the result of laboratory investigation, the question is raised whether or not we should give up all animal experimentation and await the results of clinical studies. While it is perfectly obvious that the final answer as to the value of chemotherapy in the prophylaxis and the treatment of gas gangrene can come only after extensive clinical study, it is equally apparent that there is much to be learned from further animal experimentation. From time to time in this report we have suggested possible avenues for additional study which should be used not only with the chemotherapeutic agents already available but with additional ones as they are discovered. Further studies, however, should be coordinated so that comparisons can be made both with other laboratory experiments and with clinical observations. Much reduplication of effort would be eliminated if those interested in experimental as well as clinical gas gangrene would agree on the most suitable approach to the experimental problem.

#### CONCLUSIONS

While there are considerable data on the use of the newer chemotherapeutic agents in the treatment of experimental gas gangrene, there is lack of agreement among the various observers as to the value of these agents. Correlation of the results reported in the literature is made difficult because of a lack of uniformity in methods.

A method is presented for the production in experimental animals of wounds contaminated with the species of clostridia associated with clinical gas gangrene. These wounds simulate acute traumatic wounds in human beings and if untreated lead in a large proportion of the animals to the development of gas gangrene and death.

When used in such experimental wounds within two hours after production and contamination, sulfanilamide, sulfadiazine, sulfathiazole and the sodium salts of the latter two are effective in the prevention of death from gas gangrene in animals whose wounds are contaminated with either *Cl. welchii* or *Cl. septicum*. The effectiveness of zinc peroxide in such wounds has not been convincingly demonstrated by our experiments.

Under the same conditions zinc peroxide is effective in producing a slight but statistically significant reduction in mortality from gas gangrene in animals with *Cl. novyi*-contaminated wounds. Sodium sulfathiazole approaches zinc peroxide in effectiveness, but the reduction in mortality is not statistically significant. Complete failure was encountered with the other sulfonamide compounds in *Cl. novyi*-contaminated wounds.

None of the chemotherapeutic agents studied were effective in preventing death from gas gangrene in animals whose experimental traumatic wounds were contaminated with *Cl. sordellii*. Yet sulfadiazine, sulfathiazole and their sodium salts were effective in producing significant delay in death from gas gangrene.

In animals with *Cl. welchii*-contaminated wounds, debridement and irrigation of the wounds in addition to chemotherapy are of significantly greater value than the use of chemotherapy alone. However, debridement and irrigation without chemotherapy gave results not significantly different from those obtained in the untreated controls.

In general, sulfadiazine, sulfathiazole and their sodium salts are more effective in preventing experimental gas gangrene than is sulfanilamide. Except in the *Cl. novyi*-contaminated wounds there is no significant difference between sulfathiazole and its sodium salt; however, sodium sulfadiazine appears to be superior to sulfadiazine.

A standard type of wound and uniform method of approach are needed so that further experimentation can go forward on a basis suitable for making comparisons. Since the results in this problem have a direct clinical application, experiments should as closely as possible mirror clinical conditions.

We have attempted to point out the complexity of the problem and have emphasized the fact that the multiplicity of the factors involved may considerably alter the results obtained. There should be a consensus among investigators in this field in order that the experimental methods may be standardized with regard to the lesion produced, the contaminating organisms to be used, the dosage and the method of administration of the treatment to be instituted, the experimental animals to be employed and the criteria to be used in determining the results.

The discrepancies in the results so far obtained in experimental gas gangrene clearly indicate that further studies must be carried out before the newer chemotherapeutic agents can be properly evaluated.

180 Fort Washington Avenue.

# INTERPELVIABDOMINAL AMPUTATION

## REPORT OF THREE CASES

W. E. LEIGHTON, M.D.

ST. LOUIS

On April 19, 1935, I successfully performed a one stage interpelvi-abdominal amputation for an osteochondroma of the pelvis on a man 24 years of age. At the time of writing he is still alive and active. While I had performed interscapulothoracic amputation a number of times and had disarticulated the hip several times in the past few years, I had never had the opportunity before to perform this extremely mutilating operation, and I was somewhat at a loss as to the correct procedure. I had read about the operation as reported by Keen,<sup>1</sup> Pringle<sup>2</sup> and Judin,<sup>3</sup> but otherwise I was in the same stage of uncertainty as the French surgeon, Leriche,<sup>4</sup> who recently stated that when the occasion arose to perform this major operation, he was unfamiliar with the operation, had never done it and had never seen it done. He might also have added that it was probably true that none of his conferees were in a position to aid him.

## REPORT OF CASES

CASE 1.— F. S., a man aged 24, was admitted to the Barnard Free Skin and Cancer Hospital on April 8, 1935, with a history of having noticed a growth on the right hip about eight months before for which he consulted a physician who told him to return for observation. His physician dying shortly after, he neglected to see another. The tumor continued to grow and caused some pain, especially at night. Examination at this time revealed a large tumor on the back involving the wing of the right ilium; this was extremely painful. The Wassermann test gave a negative result, although there was a history of a chancre four years before for which the patient received eight injections. There was also a history of gonorrhea eight years previously. Otherwise he had been in good health. There was no familial history of cancer. Roentgen examination at this time showed a tumor mass involving the wing of the ilium; this was pronounced an osteogenic sarcoma.

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From the surgical service of Dr. W. E. Leighton, Barnard Free Skin and Cancer Hospital, and St. Louis University School of Medicine.

1. Keen, W. W., and da Costa, J. C.: *Internat. Clin.* 4:127, 1904.

2. Pringle, J. H.: *Lancet* 1:530, 1909; *Brit. J. Surg.* 4:283, 1916.

3. Judin, S. S.: *Surg., Gynec. & Obst.* 43:668, 1926.

4. Leriche, R., and Stuz, E.: *Presse méd.* 44:65, 1936.



Fig. 1 (case 1).—Roentgenogram showing large tumor involving the wing of the right ilium.



Fig. 2 (case 1).—Photograph of patient taken after interpelviabdominal amputation.

On April 19, with the patient under spinal anesthesia, an interpelviabdominal amputation was performed. The incision used was that described by Keen, which is somewhat similar to that of Savariaud.<sup>5</sup> Both incisions employ a long lateral musculocutaneous flap, preserving the adductor group of muscles with their attachments to the pubis and the ischium and the femoral vessel. The rami of the ischium and the pubis were divided with the Gigli saw, the attachment of the adductor muscles being preserved. The posterior incision passed around the tumor mass from the anterior superior spine to the tuberosity of the ischium, and the ilium was disarticulated. By dividing the gluteus maximus muscle and the piriformis muscle, the leg was readily removed. All large vessels were caught and ligated before severance. The lateral flap was turned outward and backward, and the muscles and the skin were approximated. A rubber dam drain was placed in the lower angle of the wound. Considerable shock followed the operation, but a blood transfusion relieved the immediate danger. There was free drainage from the wound for several days. The patient was out of bed and up in a wheel chair in about three weeks. He was around on crutches within two months. He was discharged with his wound healed soon after. The pathologic report was osteochondroma.

He has been seen repeatedly since and is in good health at the time of writing, six years after the operation.

CASE 2.—Mrs. B. F., a 44 year old woman, was admitted to St. Luke's Hospital on Oct. 22, 1939, because of swelling and pain in the right groin during the past year. The pain radiated from the right sacrosciatic region and the right hip downward.

Pelvic examination at this time revealed the uterus and the cervix incorporated in a fixed semisolid mass which was not tender. The adnexa were not palpable. The mass gave me the impression of a pelvic carcinoma.

Roentgen examination at this time showed a bony tumor arising from the brim of the pelvis and projecting into the cavity of the pelvis. A chest plate did not reveal any pulmonary involvement. A diagnosis of osteosarcoma was made. Biopsy performed on October 23 revealed chondrosarcoma.

The serious nature of the disease was explained to the patient, and she consented to a radical amputation. On November 8, an interpelviabdominal amputation was performed according to the technic of Judin, which consists in making a large posterior lateral flap, preserving the gluteus maximus muscle which gives a firm muscular support for the abdomen.

In the week between biopsy and operation a considerable infiltration of the tissues at the site of incision occurred; this illustrates the danger of delaying operation following biopsy.

There was considerable shock; this had been anticipated by a transfusion of 500 cc. of blood on two previous alternate days. A postoperative transfusion of 500 cc. of blood improved her condition. The blood pressure the following day was 100 systolic and 80 diastolic. The pulse was of fair quality. The wound drained freely, and the stitches were removed on the twelfth day. About one month later there was a suspicious-looking area in the upper part of the wound which on biopsy was diagnosed as chondrosarcoma. The general condition grad-

5. Savariaud: *Rev. de chir.* 26:345, 1902.

ually grew worse, and the patient died on Jan. 7, 1940, just two months after the operation. At autopsy the growth was shown to have spread from the pelvis along the vessels to the lungs, which were involved in the metastasis.



Fig. 3 (case 2).—Roentgenogram showing a bony tumor arising from the brim of the pelvis and projecting into the cavity.



Fig. 4 (case 3).—Roentgenogram showing a tumor of the left ischium involving the ramus to the margin of the acetabulum.

CASE 3.—J. R., a 47 year old man, entered St. Mary's Hospital on May 12, 1941. He had received a severe jolt while riding horseback ten days previously. He struck the cantle of the saddle so hard that he thought he had broken his

leg. He went home and consulted his family physician. Examination at that time did not show a palpable tumor but did reveal some tenderness in the region of the ischium. Roentgen examination revealed a tumor of the left ischium involving the ramus to the margin of the acetabulum.

A diagnosis of osteogenic sarcoma was made. Palliative treatment by irradiation not being successful in these cases, radical amputation was advised. This the patient accepted, and on May 14 an interpelviabdominal amputation was performed with the patient under both spinal and general anesthesia, the latter induced with ether. The technic employed was that described by Judin, the details of which I shall presently describe. The pathologic report was osteosarcoma. There was little shock; however, 500 cc. of blood was given. The patient made a good recovery from the operation. There was free drainage. The stitches were removed on the twelfth day. The patient was out of bed and using crutches on June 2 and was discharged from the hospital on June 5. He was seen on December 9. He had gained in weight, was going about on crutches and driving his automobile.

#### COMMENT

The hindquarter amputation, known most commonly as the interilioabdominal amputation, has been given various names, such as hemipelvectomy, interinominoabdominal amputation, interpelviabdominal amputation and interiliosacropubic disarticulation. While interinominoabdominal amputation would seem to be the correct term, I have used the title interpelviabdominal amputation, adopted by the Committee on Surgical Nomenclature of the Western Surgical Association.

Since the first interpelviabdominal operation by Billroth in 1891, there have been recorded in the literature 108 operations. In the first 21 cases reported by Ransohoff,<sup>6</sup> there was a mortality rate of 75 per cent, most of the deaths occurring on the operating table or shortly after operation. In a report by Pringle of a comparable number of cases, a total mortality rate in 42 cases was 58.1 per cent; and in the tabulation by Gordon-Taylor<sup>7</sup> of 79 cases in 1934, the mortality rate remained over 50 per cent.

Since 1935 I have successfully performed the interpelviabdominal amputation 3 times. There have been reports of 19 similar operations, 17 of which I have reviewed. Two reports from the Russian literature were not obtained. There were 3 deaths in the series. For the total verified 20 cases, the mortality rate was 15 per cent, a striking difference in comparison with any of the previous reports.

The indications for this rarely used procedure have been primary tumors, either benign or malignant, of the femur, the thigh or the pelvis, metastatic growths of the pelvis and tuberculous or nontuberculous osteomyelitis of the hip, the pelvis or both. It is an operation with a high initial mortality rate; shock and prolonged suppuration are the chief

6. Ransohoff, J.: *Ann. Surg.* 50:925, 1909.

7. Gordon-Taylor, G., and Wiles, P.: *Brit. J. Surg.* 22:671, 1934.



causes of early death. For this reason it should be undertaken only after serious consideration of the physical condition of the patient and the measures to combat shock. As one author stated, "it is the most colossal mutilation that can be inflicted on the human body."

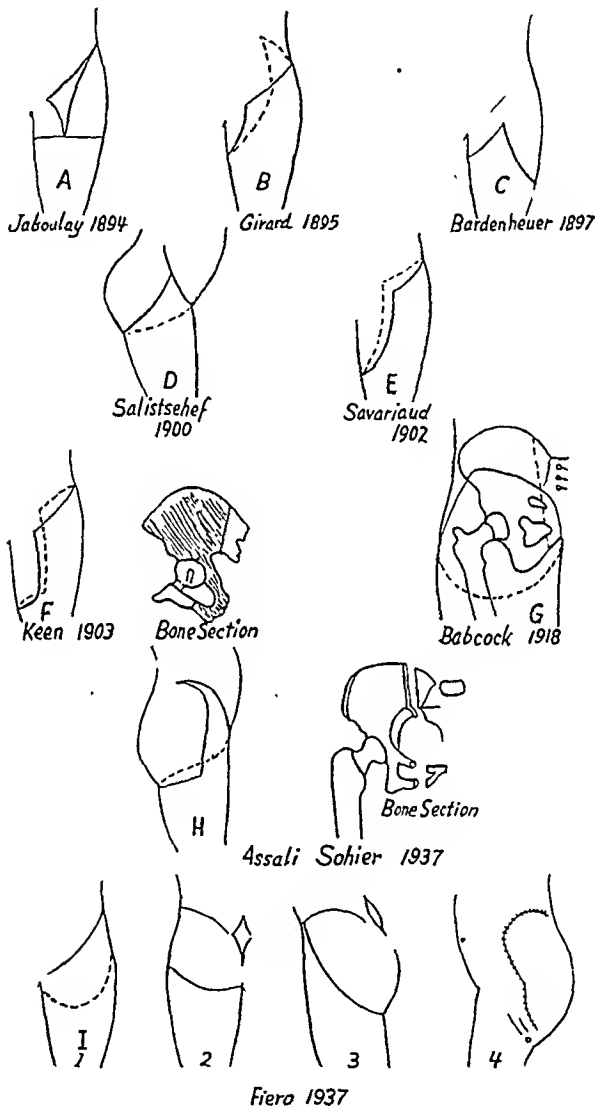


Fig. 5.—Chart showing incisions used by various authors for interpelvi-abdominal amputation.

In a few instances an amputation at the hip or the thigh has preceded division of the pelvic bone, but in the large majority of cases a one stage operation has been employed.

## DESCRIPTION OF THE OPERATION

The operation, described by Salistschef and somewhat modified since, consists principally of the formation of an external or gluteal flap, a satisfactory operation in many cases. It may be divided into two stages.

*First Stage.*—With the patient on his back, the incision is begun at the posterior superior spine of the ilium and is extended by following along the crest and the ilioinguinal ligament nearly to the spine of the



Fig. 6.—A, B, C and D, drawings showing incision for reflecting the abdominal wall with the peritoneum, ligature of the external iliac artery and vein and the line of division of the pubis; E, lateral incision with reflection of the gluteus maximus muscle to expose the sciatic plexus and the gluteal artery and division of the ilium (redrawn after the method of J. Assali and H. Sohler [J. de chir. 50:310, 1937]).

pubis. It is then curved downward on the inner part of the thigh to the gluteal groove. The abdominal muscles are divided at their origin from the crest of the ilium, and the ilioinguinal ligament is divided at each end. The iliac vessels are then exposed. The artery is ligated

TABLE 1.—Cases of Interpelviabdominal Amputation Reported in the Literature

Author	Year	Sex of Patient	Age of Patient, Yr.	Disease	Anesthesia	Result
Billroth, cited by Savariaud: Rev. de chir. <b>26</b> : 350, 1902	1891	..	..	.....	.....	Died in few hours
Jaboulay: Lyon méd. <b>75</b> : 507, 1894	1894	..	..	Sarcoma of femur	General	Died following day
Jaboulay, cited by Gayet: Province méd. <b>9</b> : 34 and 397, 1895	1895	M	66	Sarcoma of pelvis	.....	Died 36 hours later
Cacciopoli: Riforma med. <b>10</b> (pt. 2): 819-831, 1894	1894	M	17	Sarcoma of femur	.....	Died 3 hours later
Girard: Rev. de chir. <b>15</b> : 952, 1895	1894	F	17	Sarcoma of femur and pelvis	General	Alive after 7 mo.; metastasis
Girard: Rev. de chir. <b>18</b> : 1141, 1898	1895	M	15	Tuberculosis	.....	Died in 5 minutes
Girard: Rev. de chir. <b>18</b> : 1141, 1898	1897	M	52	Sarcoma of femur and pelvis	.....	Alive after 6 mo.; metastasis
Bardenheuer: Ber. ü. d. deutsch. Gesellsch. f. Chir. <b>26</b> : 132, 1897	1897	F	46	Tuberculosis	.....	Lived 10 mo. or more
Kocher: Text-Book of Operative Surgery, translated by H. J. Stiles, London, A. & C. Black, 1903	1898	M	..	Sarcoma of pelvis	.....	Death
Faure: Rev. de gynéc. et chir. abdom. <b>3</b> : 713, 1899; cited by Savariaud	1899	F	16	Sarcoma of pelvis	.....	Died 1 day later
Salistcheff: Arch. f. klin. Chir. <b>60</b> : 57, 1900	1899	M	38	Sarcoma of femur	General	Lived
Freeman: Ann. Surg. <b>33</b> : 318, 1901	1899	F	38	Sarcoma of femur	.....	Lived 16 mo. or more
Kadjan: Lystopsis russ. chir. 1900, vol. 4; abstracted, Jahresb. f. Chir. <b>2</b> : 1104, 1902	1900	M	25	Sarcoma of femur	General	Died 2 days later
Nanu: Rev. de chir. <b>26</b> : 365, 1902	1900	M	50	Myxosarcoma of pelvis	General	Died 20 days later from gangrene
Pringle: Lancet <b>1</b> : 530, 1900	1900	F	10	Tuberculosis of hip	.....	Lived 14 years
Pringle: Lancet <b>1</b> : 530, 1900	1906	M	Adult	Tuberculosis of hip and pelvis	.....	Died after 14 hr.
Pringle: Lancet <b>1</b> : 530, 1900	1908	M	18	Sarcoma of femur	Spinal (2/12/08)	Alive after 5 mo.; metastasis
Pringle: Brit. J. Surg. <b>4</b> : 283, 1916	1915	M	34	Sarcoma of femur	.....	Lived
Pringle: Brit. J. Surg. <b>4</b> : 283, 1916	1915	F	46	Sarcoma of femur	Spinal (8/3/15)	Lived
Gallet: J. de chir. et ann. Soc. belge de chir. <b>1</b> : 569, 1901	1901	M	25	Tuberculosis	.....	Died 6 hr. later
Gallet: J. de chir. et ann. Soc. belge de chir. <b>1</b> : 569, 1901	1901	F	39	Sarcoma of femur	.....	Died same day
Savariaud: Rev. de chir. <b>26</b> : 345, 1902 (quotes Girard and previous authors)	1901	F	7	Sarcoma of pelvis	.....	Died 2 hr. later
Mikhaloff: Kbirurgiya <b>11</b> : 471, 1902; cited by Judin <sup>3</sup>	1902	..	..	Tuberculosis	General	Died ¾ hr. later
Morestin: Bull. et mém. Soc. anat. de Paris <b>4</b> : 795, 1902	1902	F	?	Sarcoma of pelvis	.....	Died 9 hr. later
Morestin: Bull. et mém. Soc. de chir. Paris <b>34</b> : 1060, 1903	1905	M	?	Tuberculosis	.....	Lived 3 yr. or more
Morestin: Bull. et mém. Soc. anat. de Paris <b>11</b> : 288, 1909	1909	M	35	Tuberculosis	.....	Died 14 hr. later
DeRuyter, cited by Meyer, H.: Ein Beitrag zur Exarticulation inter-ilio-abdominalis, Inaug. Dissert., Leipzig, 1902	1902	M	45	Sarcoma of femur	.....	Died 1 hr. later
Ribera, cited by Simon: Siglo méd. <b>1</b> : 779, 1903	1902	?	8	Tuberculosis	.....	Died 8 days later from gangrene
Ribera, cited by Simon: Siglo méd. <b>1</b> : 779, 1903	1902	?	8	Tuberculosis	.....	Died soon after
Ribera, cited by Simon: Siglo méd. <b>1</b> : 779, 1903	1902	F	10	Tuberculosis	.....	Died 3 hr. later
Christel, cited by Driest: Deutsche Ztschr. f. Chir. <b>71</b> : 4, 1904	1903	F	2	Tuberculosis	.....	Lived

TABLE 1.—Cases of Interpelviabdominal Amputation Reported  
in the Literature—Continued

Author	Year	Sex of Pa- tient	Age of Pa- tient, Yr.	Disease	Anesthesia	Result
Keen and DaCosta <sup>1</sup> .	1903	M	42	Sarcoma of pelvis	.	Died 33 hr. later
Verncuil: J. de chir. et ann. Soc. belge de chir. 5:406, 1905	1905	.	.	Tuberculosis	.	Died 2 hr. later
Lastaria: Riforma med. 23:457, 1907	1906	M	22	Chondrosar- coma	.	Died on table
Orloff: Vestnik khir 2:225, 1901; abstracted, Jahreshb. u. d. Fortschr. a. d. Geb. d. Chir. 7:1104, 1907	1907	M	47	Sarcoma of femur and pelvis	.	Died 35 days later from sepsis
Bier: Deutsche med. Wchn- schr. 35:45, 1909	1908	M	45	Sarcoma of pelvis	Spinal	Lived 2 mo
Sinakevitich: Khirurgiya 27: 60, 1910; cited by Judin <sup>2</sup>	1908	M	47	Sarcoma of femur and pelvis	.	Died a few hours later
Krynsky: abstracted, Zen- tralbl. f. Chir 37:1132, 1910	1908	.	.	Sarcoma of femur and pelvis	Spinal	Alive after 5 wk.: cachexia
Pagenstecher: Arch. f. klin. Chir. 90:169, 1909	1909	F	50	Sarcoma of pelvis	.	Lived 3 mo. or more
Ransohoff: Ann. Surg. 50: 925, 1909	1909	M	45	Sarcoma of pelvis	General	Died 4 wk. later from enterocolitis
Roux, cited by Plantard: Arch. prov. de chir. 18: 657, 1909	1909	M	40	Sarcoma	.	Lived 3 mo. or more
Axhausen: Arch. f. klin. Chir. 91:538, 1910	1910	F	45	Sarcoma	General	Died 9 hr. later
Krim: Khirurgiya 34:763, 1913; cited by Judin <sup>2</sup>	1913	F	27	Sarcoma of pelvis	General	Died 13 days later
Gaudier: Bull. et mém. Soc. de chir. de Paris 39: 1570, 1913	1913	M	15	Nontuberculous osteomyelitis	.	Lived
Babeock: Surg., Gynec. & Obst. 26:554, 1918	1914	M	28	Marjolin ulcer	.	Lived 4 mo
Babeock: Surg., Gynec. & Obst. 26:554, 1918	1915	F	56	Sarcoma of pelvis	.	Lived 10 weeks
Babeock: Surg., Gynec. & Obst. 26:554, 1918	1916	M	52	Marjolin ulcer	.	Died shortly after operation
Babeock: Textbook of Sur- gery, Philadelphia, W. B. Saunders Company, 1928	.	.	.	.	.	.
Babeock: Textbook of Sur- gery, Philadelphia, W. B. Saunders Company, 1928	.	.	.	.	.	.
Maffei: Proc. Soc. internat. de chir. orthop., 1933, p. 270	1915	F	5	Tuberculosis of hip	.	Well 17 yr. later
Maffei: Proc. Soc. internat. de chir. orthop., 1933, p. 270	1915	M	8	Tuberculosis of hip	.	Lived 1 mo.
Maffei: Proc. Soc. internat. de chir. orthop., 1933, p. 270	1915	.	3	Tuberculosis of hip	.	Died 2 hr. later
Loeffler: Ztschr. f. orthop. Chir. 39:305, 1919	1918	M	11	Sarcoma of pelvis	.	Lived 15 mo. or longer
Bergmann, cited by Judin <sup>2</sup>	1918	..	..	Nontuberculous osteomyelitis	.	.. . . .
Bergmann, cited by Judin <sup>2</sup>	1918	.	.	Nontuberculous osteomyelitis	.	.. . . .
Bergmann, cited by Judin <sup>2</sup>	1918	.	.	Nontuberculous osteomyelitis	.	.. . . .
Bergmann, cited by Judin <sup>2</sup>	1918	.	.	Nontuberculous osteomyelitis	.. . .	.. . . .
Bergmann, cited by Judin <sup>2</sup>	1918	..	..	Nontuberculous osteomyelitis	.. .	.. . . . . . .
Smirnov, cited by Judin <sup>2</sup>	1919	M	33	Tuberculosis	.....	Died on table
Toprover-Krimov: Ekateri- nos lav. M. J. (no. 1) 2: 44, 1925; cited by Judin <sup>2</sup>	1919	M	47	Sarcoma of femur	General	Alive after 2 mo.: metastasis to lung
Veinshall: Nov. khir. 3:147, 1925; cited by Judin <sup>2</sup>	1921	M	25	Sarcoma of pelvis	General	Died 27 days later from parotitis and pneumonia
Brzozowski: Novy khir. Arkh. 4:179, 1921; cited by Judin <sup>2</sup>	1921	F	16	Sarcoma of femur	General	Alive after 4 mo.: metastasis
Israel, cited by Judin <sup>2</sup> ...	1921	F	..	Sarcoma	.	Died ½ hr. later
Schadelmosc: Acta chir. Scandinav 53:523, 1924	1923	..	.	Chondrosar- coma	...	Lived 10 mo. or more

TABLE 1.—Cases of Interpelviabdominal Amputation Reported  
in the Literature—Continued

Author	Year	Sex of Pa- tient	Age of Yr.	Disease	Anesthesia	Result
Judiu <sup>3</sup> .....	1923	F	36	Chondrosarcoma of femur	Spinal	Alive after 2½ yr. or more; gave birth to a child Lived 8 weeks
Rabinovitch: Nov. khir. <b>3</b> : 394, 1925; cited by Judin <sup>3</sup>	1925	M	58	Sarcoma of femur	Spinal	Lived 8 weeks
Rabinovitch, cited by Judin <sup>3</sup>	1925	M	49	Sarcoma of femur	Spinal	Died 3 days later
Krassintzev, cited by Judin <sup>3</sup>	1925	M	..	Sarcoma of femur	General	Died 8 days later
Krassintzev, cited by Judin <sup>3</sup>	1925	M	..	Sarcoma of femur	General	Died 30 days later
Krassintzev, cited by Judin <sup>3</sup>	1925	M	..	Sarcoma of femur	General	Died 2 days later
Krassintzev, cited by Judin <sup>3</sup>	1925	M	45	Sarcoma of pelvis	Chloral hydrate	Died 5 hr. later
Krassintzev: Moscow S. Soc. 1925; cited by Judin <sup>3</sup>	1925	M	43	Chondrosarcoma of femur	Spinal	Lived
Kokln, cited by Judin <sup>3</sup> ....	....	F	30	Sarcoma of pelvis	Spinal	Died 18 hr. later
Rosanov, cited by Judin <sup>3</sup> ..	....	F	27	Tuberculosis	General	Died 6 hr. later
Rosanov, cited by Judin <sup>3</sup> ..	....	M	25	Sarcoma of pelvis	Spinal	Alive after 3 mo.; metastasis
Rosanov, cited by Judin <sup>3</sup> ..	....	M	50	Sarcoma	Spinal	Died 5 days later
Czerny, cited by Judin <sup>3</sup> ....	....	..	..	..	..	..
Goldberg, cited by Judin <sup>3</sup>	....	..	..	..	..	..
Abrashanow, cited by Rls- waseh: Deutsche Ztschr. f. Chir. <b>238</b> : 121, 1932	....	F	35	Sarcoma of femur	Spinal	Lived 3 mo. or more
Speed: Ann. Surg. <b>95</b> : 167, Sept. 1932	1931	M	59	Sarcoma of pelvis	Ether	Died at end of operation
Speed: Ann. Surg. <b>95</b> : 167, Oct. 1932	1931	M	45	Sarcoma of femur and pelvis	Spinal	Died 1 hr. later
Gordon-Taylor: Brit. Surg. <b>22</b> : 671, 1934	J. 1922	M	25	Round-cell sarcoma of femur	Spinal	Died 6 hr. later
Gordon-Taylor: Brit. Surg. <b>22</b> : 671, 1934	J. 1929	M	17	Osteoclastoma	Spinal	Lived 5½ yr. or more Lived
Gordon-Taylor: Brit. Surg. <b>22</b> : 671, 1934	J. 1933	M	59	Chondrosarcoma of pelvis	Spinal	Lived
Gordon-Taylor: Brit. Surg. <b>22</b> : 671, 1934	J. 1934	M	28	Sarcoma of pelvis	Spinal	Died 2½ hr. later
Gordon-Taylor: Brit. Surg. <b>22</b> : 671, 1934	J. 1934	M	18	Sarcoma of femur	Spinal	Lived
Gordon-Taylor: Brit. Surg. <b>27</b> : 643, 1940	J. 1935	M	17	Sarcoma of muscles of Scarpa's triangle	General	Lived
Gordon-Taylor: Brit. Surg. <b>27</b> : 643, 1940	J. 1936	F	37	Osteolytic sarcoma of ilium	General	Died a few hr. later
Gordon-Taylor: Brit. Surg. <b>27</b> : 643, 1940	J. 1937	F	25	Sarcoma of muscles of Scarpa's triangle	General	Lived
Gordon-Taylor: Brit. Surg. <b>27</b> : 643, 1940	J. 1938	M	14	Sarcoma of right innominate bone	General	Lived
Gordon-Taylor: Brit. Surg. <b>27</b> : 643, 1940	J. 1938	M	34	Sarcoma of right psoas muscle	General	Died a few hr. later
Gordon-Taylor: Brit. Surg. <b>27</b> : 643, 1940	J. 1939	M	26	Chondrosarcoma of left innominate bone	General	Lived
Fitzgerald: J. Bone & Joint Surg. <b>18</b> : 402, 1936	1935	M	13	Osteogenic sarcoma of femur	Spinal	Lived
Leriche and Stulz: Presse méd. <b>44</b> : 65, 1936	1935	M	33	Chondromyxosarcoma of pelvis	.....	Lived
Leriche and Stulz: Mém. Acad. de chir. <b>64</b> : 31, 1938	1937	M	30	Ewing sarcoma of femur	.....	Lived
Pascalls: Progrès méd., 1936, p. 1481	1936	M	44	Osteosarcoma of pelvis	.....	Lived
Banet and Noho: Bol. lig. contra el cancer <b>11</b> : 43, 1936	1936	M	27	Fibrosarcoma of femur	Ether	Lived
Gersh: Sovet. khir., 1936, no. 4, p. 681	1936	..	..	..	..	..

TABLE 1.—*Cases of Interpelviabdominal Amputation Reported in the Literature—Continued*

Author	Year	Sex of Patient	Age of Patient, Yr.	Disease	Anesthesia	Result
Fiero: Cir. y cirujanos 5: 169, 1937	1936	F	..	Sarcoma of femur	.....	Lived
Fitzwilliams: Proc. Roy. Soc. Med. 31: 548, 1938	1937	M	62	Rhabdomyosarcoma of vastus internus muscle	.....	Lived
Richard and Clavel: Lyon chir. 35: 81, 1938	1938	M	36	Sarcoma of femur	Ether	Died
Rapant: Chirurg 10: 804, 1938	1938	M	29	Osteosarcoma of femur	.....	Lived
Rapant: Chirurg 10: 804, 1938	1938	M	14	Osteosarcoma of femur	Ether	Lived
Shyart: Vestnik klin. 55: 57, 1938	1938	M				
Padovani: Mém. Acad. de chir. 65: 361, 1939	1938	M	18	Myeloma of femur; single trauma	Ether	Lived
Leighton: Bull. St. Louis M. Soc., 1938, p. 87	1935	M	22	Osteochondroma of pelvis	Spinal	Living after 6 yr.
Leighton: Present report..	1939	F	44	Chondrosarcoma of pelvis	Spinal	Lived 2 mo.; pulmonary metastasis
Leighton: Present report..	1941	M	47	Osteosarcoma of ischium	Spinal	Living

and the leg elevated in order to return the blood of the leg into the body, a method suggested by Webb-Jones in 1899. This may be assisted by the application of a Martin bandage. The vessels with parietal peritoneum are readily reflected together with the ureter to the brim of the pelvis. At this point the pubic bone may be separated at the symphysis or divided with a Gigli saw. A Gigli guide or a curved Rochester-Péan forceps is readily passed behind the pubic bone. The Gigli saw is pulled through and the bone divided. By keeping close to the bone there is little danger of injuring the internal pudendal artery.

*Second Stage.*—With the patient turned on his sound side, a posterior flap from the middle of the crest of the ilium beginning at the first incision is formed by an incision which extends downward over the trochanter major and about 3 inches (8 cm.) below to reach the insertion of the gluteus maximus muscle in the femur. It then curves backward to meet the first incision which has been extended outward in the gluteal groove. The fascia is divided in the same line, and the gluteus maximus muscle is readily exposed, divided at its insertion to the femur and reflected outward. Care must be taken to avoid injury to the superior gluteal artery and nerve, which supply this muscle. When the greater sciatic notch is reached, the piriformis muscle is observed crossing this space. Division of the muscle allows one to recognize the sciatic plexus of nerves and preserve the branches to the gluteus maximus muscle and also the superficial branches of the gluteal artery. The deep branches of the superior gluteal artery which pass under the gluteus medius and gluteus minimus muscles are readily located, ligated and divided, and the corresponding muscles are readily freed from the ilium. Into the sciatic plexus, which is exposed emerging from below the

piriformis muscle, procaine hydrochloride is injected, and it is then divided. The inferior gluteal and internal pudendal arteries are ligated at this time. By separating the iliopsoas muscle from the ilium, a Gigli saw is passed over the ilium through the sacrosciatic notch and the bone divided parallel to the sacroiliac articulation. The remaining attachments are the sacrosciatic ligaments, and the iliopsoas and levator ani muscles, the division of which frees the extremity from the body. The obturator vessels and nerve usually require attention at this point in the operation. The large gluteal flap is brought into place, and the upper portion of the muscle is sutured to the abdominal muscles and the lower portion to the levator ani. The tendon is attached to the remnant of the adductor muscle at the pubis. A drain is placed in the lower angle. A few silkworm gut tension sutures and skin closure with silk or clips complete the operation.

TABLE 2.—*Summary of Diseases for Which Interpelviabdominal Amputation Was Done and Operative Results*

Disease	Patients	Lived	Died	Result Unknown	Operative Mortality Rate
Sarcoma.....	73	39	34	..	....
Tuberculous osteomyelitis.....	18	6	12	..	....
Nontuberculous osteomyelitis..	6	3	3	..	....
Osteochondroma.....	2	2	0	..	....
Marjolin ulcer.....	2	1	1	..	....
Not stated.....	7	..	1	6	....
Total.....	108	51	51	6	50%

Table 1 incorporates all the published cases of interpelviabdominal amputation.<sup>7a</sup> The list of Judin contained several reduplications, and a list by Gordon-Taylor had omitted 2 cases reported by Babcock. I have reviewed the original papers so far as possible, and with these corrections I find that the operation has been done 108 times. The cases are arranged according to date of operation, and when more than 1 case has been reported, I have listed the authors in sequence.

In table 2 I have given a brief summary of the diseases for which the amputation was done and the results of the operation.

Geschickter and Copeland<sup>8</sup> in their book on bone tumors published in 1931 collected 155 cases of chondromyxosarcoma. In 8 of these the

7a. Since my paper was submitted for publication, I have found the following references to similar operations: Turner, G. G.: *Proc. Roy. Soc. Med.* **34**:562, 1941. Selig, S.: *J. Bone & Joint Surg.* **23**:929, 1941. Whittaker, A. H., and Sobin, D. J.: *Ann. Surg.* **115**:435, 1942. Morton, J. J.: *Ann. Surg.* **115**:628, 1942.

8. Geschickter, O. F., and Copeland, M. M.: *Tumors of Bone*, New York, American Journal of Cancer, 1932.

tumor was primary in the innominate bone. Seven patients died following palliative treatment, such as curettement, excision or irradiation. One was living at the end of twenty months. Among 88 cases of osteosarcoma collected Geschickter and Copeland found only 1 case in which the growth arose in the os pelvis, and in this case the patient did not survive palliative treatment.

On analyzing the 108 cases of interpelviabdominal amputation I find that the operation has been performed for sarcoma 73 times. In 27 cases the disease was primary in the os pelvis. Thirteen patients recovered and lived from two months to five years or more. Fourteen patients died, most of them within a few hours; the mortality rate is thus 51.85 per cent.

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# IMPORTANCE AND DISTRIBUTION OF THE TRANSVERSALIS FASCIA FROM THE VIEWPOINT OF THE SURGEON

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CHICAGO

The importance of the transversalis fascia can scarcely be exaggerated. How it has escaped the emphasis it deserves is inexplicable. Few anatomists have seen it complete. Fewer surgeons appreciate its existence. Books on anatomy dismiss the graphic description of this relatively all-pervading abdominal tissue with one paragraph. Yet the transversalis fascia in its entirety is second in importance perhaps only to the peritoneum as an encasing membrane of the abdominal contents—now reenforcing, now merging into one with the parietal peritoneal tissue on the one hand and with the abdominal aponeurotic fibers on the other. Where function demands, it thickens and develops its strong elastic fibers to a protective perfection.

The purpose of this paper is to describe in detail the distribution of the transversalis fascia as observed in a large series of dissections on cadavers carried out over a period of seven years. It is likewise desired to emphasize several points not generally appreciated.

Bassini was one of the first to call attention from a surgical standpoint to the importance of the transversalis fascia in the region of the inguinal canal. It was he who emphasized the part played by this fascia in the production and the repair of inguinal hernia. The fibers here are usually strong and form the posterior surface, or surgical floor, of the inguinal canal. They conify (fig. 1) and thicken to produce the internal inguinal ring and descend over the structures of the cord in a funnel-shaped manner to constitute what is known as the infundibuliform fascia.

Superiorly, from the inguinal canal, the fascia spread out laterally and upward, ascending anteriorly over the entire under surface of the abdominal muscular wall until it meets the thin inner fascial covering of the muscles constituting the diaphragm. Here the fibers of the transversalis fascia thin out and join so intimately with the inner fascial lining of the diaphragm that it is extremely difficult to effect separation and at times even confusing to tell definitely which sheath belongs to the proper structure. Patient and painstaking dissection, however, will



Fig. 1.—Candid camera photograph of a dissection of the inguinal region of a cadaver showing the relation of structures to the transversalis fascia.

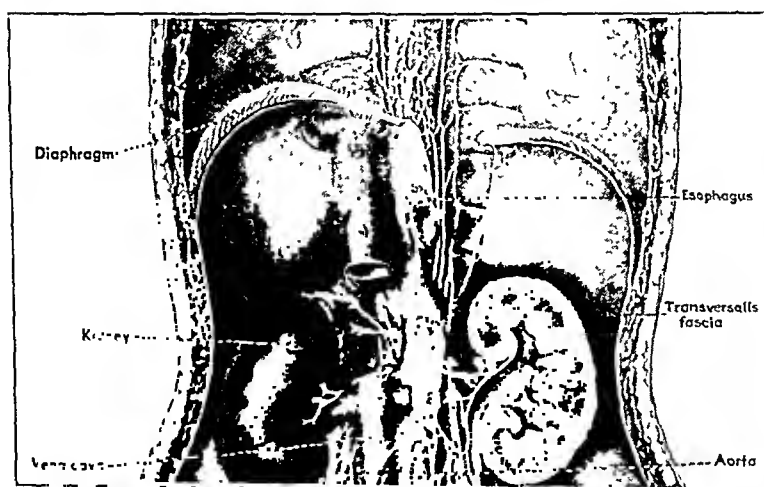


Fig. 2.—Illustration of the hiatal arrangement of the transversalis fascia. The digitation effect was produced by dissection.

reward one with the discovery of how highly specialized the protective function of the transversalis fascia is in this region.

In the center the fibers of the transversalis fascia are strongly attached and are almost one with the central fascia of the diaphragm. At each hiatal perforation, where the thoracic structures pass through to the abdomen, fibers of the transversalis fascia separate. Some ascend through the rent and travel upward several inches, encircling the tubular structures. They conify and completely encircle the perforating structures in a manner not much unlike their enclosure of the cord in the inguinal region. The other fibers descend along the perforating thoracic

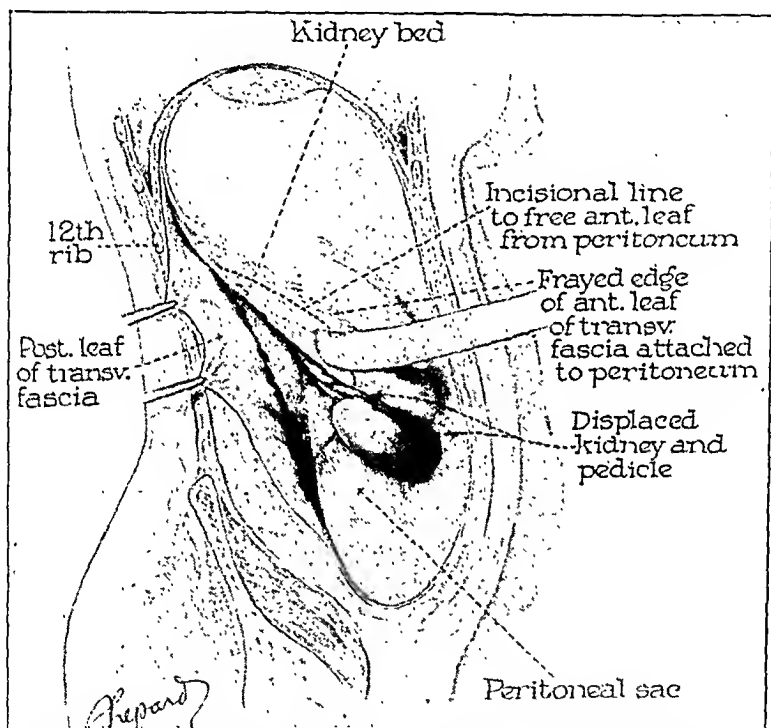


Fig. 3.—Separation of the transversalis fascia to form Gerota's fascia of the kidney.

structure, likewise encircling it in a funnel-shaped manner. Thus, the aorta, the azygos vein, the thoracic duct, the esophagus and the vena cava, the two greater and lesser splanchnic nerves and the hemiazygos vein are all surrounded and insulated by this encircling process of the transversalis fascia at their diaphragmatic hiatal perforation. The teleology is apparent and assuredly accounts for the relative infrequency of diaphragmatic hernias.

At the xyphoid process the fibers of the transversalis fascia follow the attachment of the diaphragm and merge with the fibers of the falciform ligament of the liver. Here again it is possible by careful and

assiduous dissection to separate the fibers of the transversalis fascia from the falciform ligament, and it is interesting to note the distance to which the former extend before losing their identity with the ligamentous tissue.

Posteriorly the fibers of the transversalis fascia descend over the diaphragmatic crura, giving off fibers of attachment to the lumbar vertebrae and their transverse processes and merging laterally with the aponeuroses of the psoas major and the quadratus lumborum muscles. At a level just superior to the adrenal gland the fascia splits off an

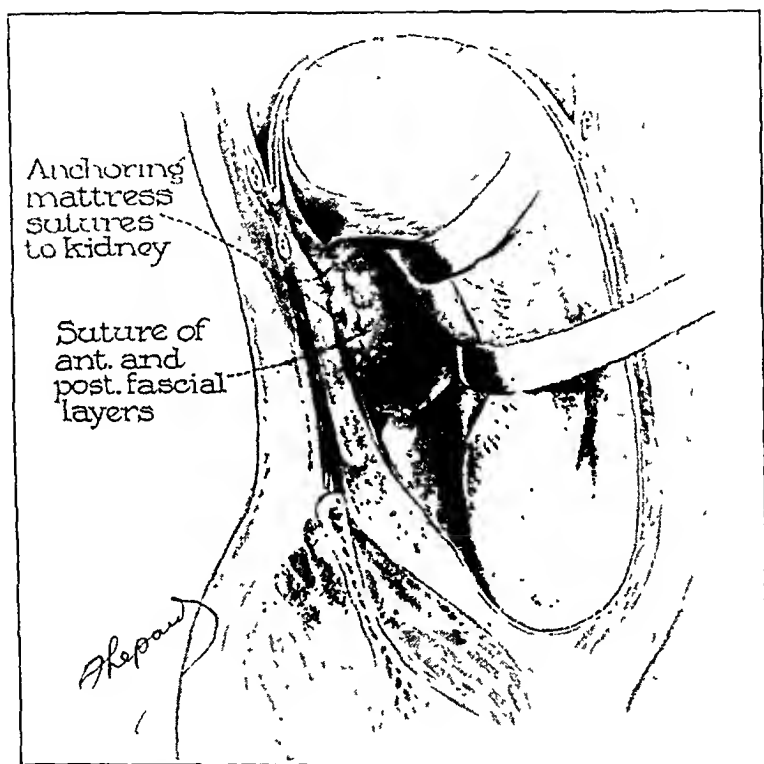


Fig. 4.—Utilization of the transversalis fascia for the surgical correction of a "floating" kidney (my method).

internal sheath which passes forward in front of the kidney and its vessels (fig. 3). This anterior sheath and the posterior sheath that descends over the psoas and quadratus muscles completely encase the kidney and form what is known as Gerota's fascia. Thus the role of the transversalis fascia is a particularly important one in the formation of the renal fossa and in the maintenance of a more or less fixed position of the kidney.

Obviously, from a surgical standpoint it can be seen that a wandering kidney is the result of imperfect fusion or relaxed attachment of this specialized structural arrangement of the transversalis fascia. The

anterior sheath is defective in its enclosing property and consequently permits the kidney to fall out of its bed. As a result, a method for nephropexy has been devised (fig. 4) the fundamental principle of which consists in simply suturing together the anterior and posterior layers of this fascia and fixing the renal capsule to one or both fascial sheaths.

If the dissection is continued posteriorly, it is possible to trace the transversalis fascia on down into the pelvis (fig. 5). Here, laterally, the fibers become almost inseparable with the aponeurotic covering of the iliac fossa, where again the fascia becomes highly specialized and warrants a separate description in all books on anatomy, under the

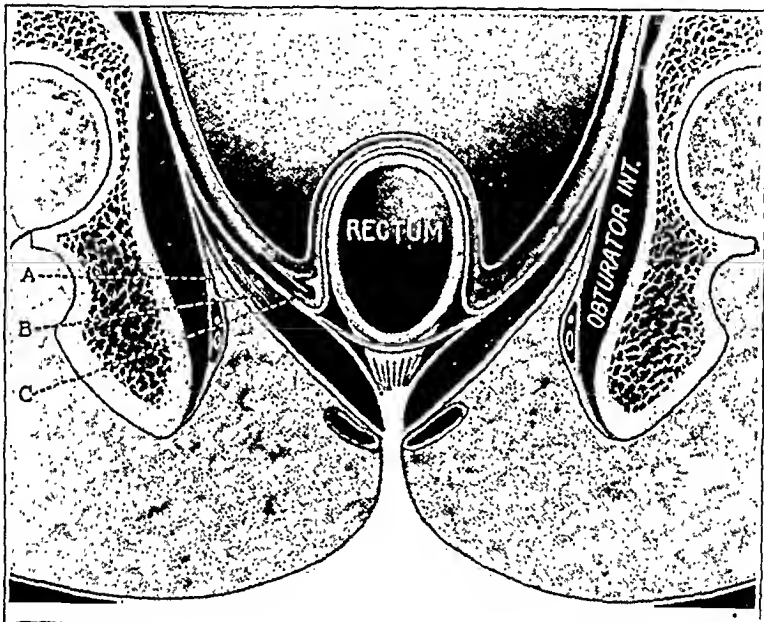


Fig. 5.—Relation of the transversalis fascia to the pelvic structures (modified from Campbell): *A*, obturator fascia; *B*, ischio-rectal fascia; *C*, rectovesical fascia.

term pelvic fascia. It forms the tendinous arch, or "white line," of the pelvis (fig. 6) by separating into several conspicuous layers, the outermost one of which is the fascial sheath of the obturator internus muscle, the obturator fascia, and loses itself by attaching to the tuberosity of the ischium. It is attached to the pubic arch and blends with the corresponding layer of the opposite side to form the posterior layer of the triangular ligament. The second, or middle, sheath, the ischio-rectal fascia, lines the under surface of the levator ani muscle, while the innermost sheath constitutes the rectovesical fascia and extends downward and inward over the upper surface of the levator ani muscle, thus completely encapsulating this structure. It then invests the bladder, the prostate and the rectum. It is the anterior and lateral reflec-

tion, or true ligament, of the bladder. It is the capsule of the prostate and covers the seminal vesicles and ducts (fig. 7). Ascending, it attaches to the inferior border of the symphysis pubis.

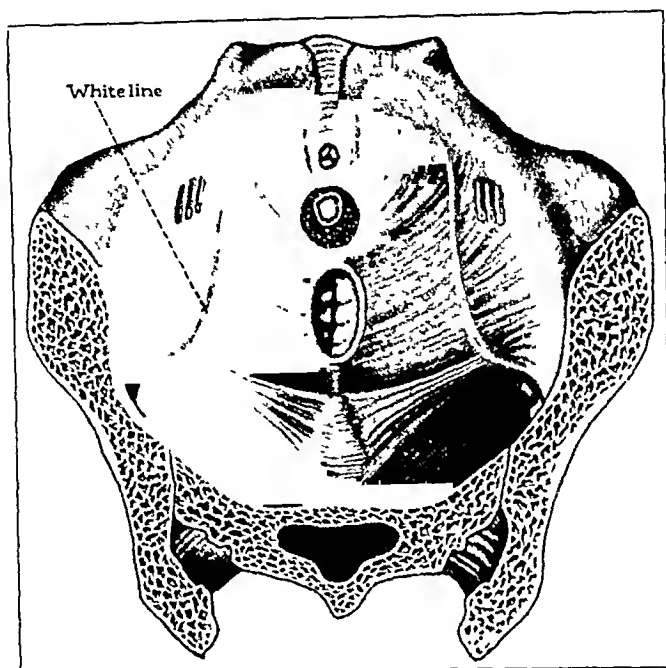


Fig. 6.—Relation of the "white line" of the pelvis to the pelvic diaphragm (modified from Campbell, W. F.: *A Textbook of Surgical Anatomy*, Philadelphia, W. B. Saunders Company, 1921).

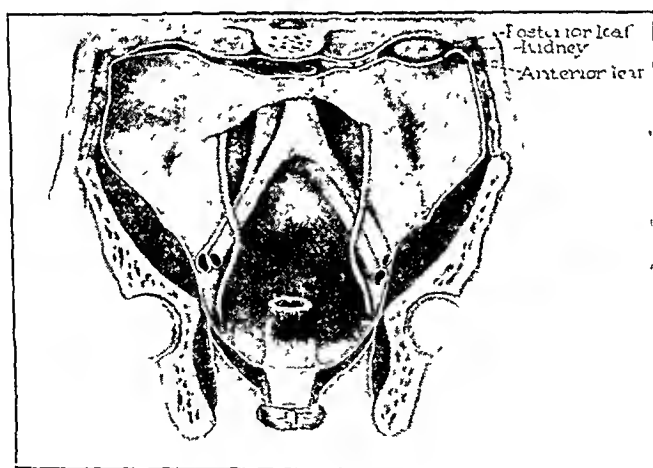


Fig. 7.—Artist's reproduction illustrating the distribution and continuity of the transversalis fascia in the pelvis—the pelvic fascia. Note the anterior and posterior leaves of the transversalis fascia forming the renal fascia.

In a woman this innermost layer, which connects the rectum and the bladder, is perforated by the vagina and the urethra; as at the

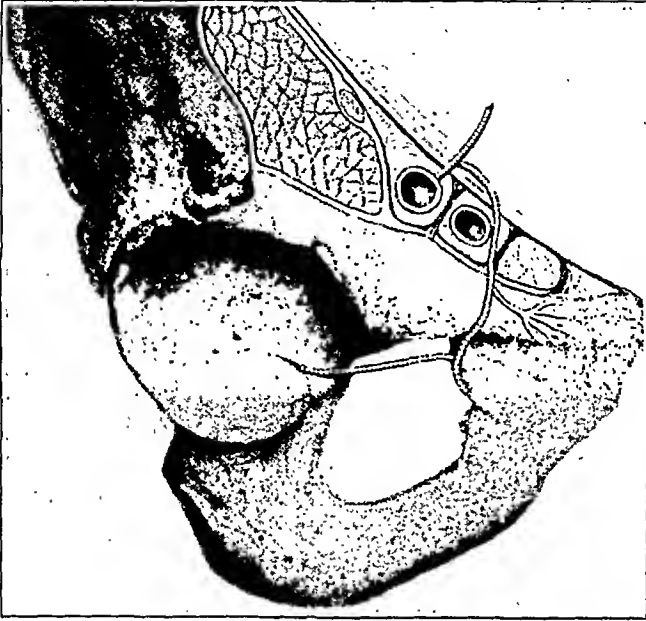


Fig. 8.—The crural arch. Note the fascial compartments and the protective arrangement for the empty space (modified from Campbell).

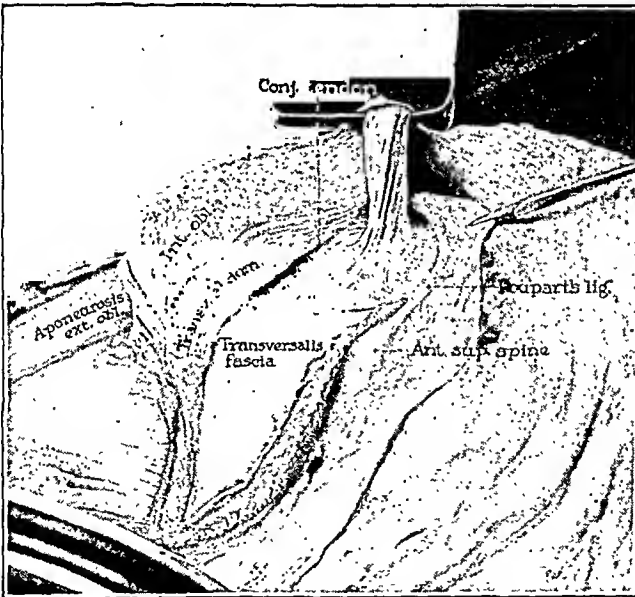


Fig. 9.—Candid camera photograph of a dissection of the inguinal region showing the relation of the transversalis fascia to Poupart's ligament. Note fibers of attachment to Poupart's ligament.

sites of other perforating organs, the fibers encircle and conify these structures, sealing off all possible exit for the pelvic organs. A disturbance in the continuity of these fibers will explain surgically the formation of perineal herniations, such as cystocele, urethrocele and rectocele.

Continuing the dissection superiorly, one finds that the fibers ascend over the posterior surface of the symphysis pubis and laterally merge with the iliopectineal fascia. Here the transversalis fascia plays an important part in relation to the structures associated with the crural arch (fig. 8). It conifies the large vessels and nerves that pass out on to the leg in an identical manner as the structures perforating the diaphragm. The fascia splits into two divisions, one ascending along the structure and the other descending, completely insulating the vessels and walling off any possible exit for an abdominal viscus. The fascia continues out to the leg, contributing to the formation of the fascia of that structure. At the femoral ring, or so-called empty space of the crural arch, the fibers of the transversalis fascia make a somewhat rosette-like arrangement that completely encloses this portion of the crural arch. Practically it can be seen that a femoral hernia at this point is acquired only by a defect in this arrangement of the fibers or by a break in their continuity. The transversalis fascia on leaving the structures beneath the crural arch gives off slivers of attachment to the inguinal ligament (fig. 9) and then spreads out to form the surgical floor of the inguinal canal, as has been described at the beginning of this paper. The description applies to both halves of the abdominal wall, and the fascia produces a continuity far beyond the expectation of the surgeon and the anatomist.

#### COMMENT

Some may dispute the nomenclature. This, however, is purely an academic question. It is conceded that it is a question for discussion. The fact remains that there is a structure in continuity with the structure admittedly called the transversalis fascia in the inguinal region and that this structure is distributed as narrated, whether one wishes to call it intra-abdominal fascia, Gerota's fascia, pelvic fascia or any other name. To restrict it, however, to the posterior sheath of the transversalis muscle, i. e. the transversus abdominis muscle, is definitely out of order and throws on the proponents of this theory the necessity of explaining, for example, the continuity of the fascia of the pelvis or the diaphragm.

Pedagogically, I believe a step forward could be taken by considering the fascia as an entity, as a simple continuity to which specific



names are affixed according to the specific location or function demanded of it (fig. 10). Assuredly it is against all principles of good pedagogy to fail to recognize the structure as a unit, generally distributed throughout the abdomen and the pelvis, and to describe it as a disjointed entity only, separate, distinct and restricted to a specialized location or property which it possesses.

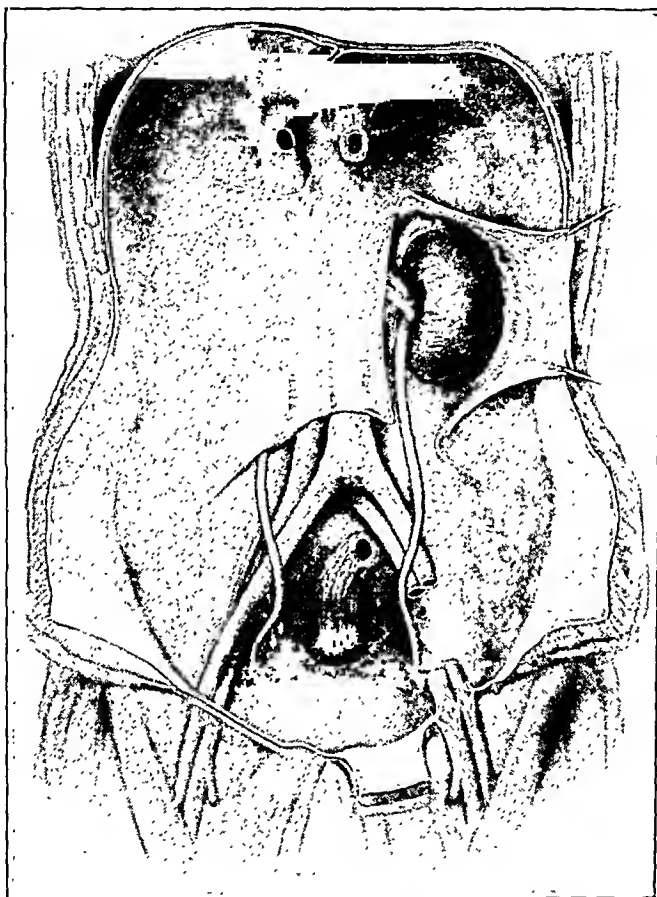


Fig. 10.—Artist's illustration of a dissection showing complete distribution and continuity of the transversalis fascia throughout the body. Note the encircling fibers about the structures that enter and leave the abdominal cavity.

#### SUMMARY

The distribution of the transversalis fascia is narrated as observed in a large series of dissections on cadavers.

Emphasis is placed on certain not generally appreciated structural features and on their teleologic function.

The possible utilization of the fascia in surgery and the advisability of a modified nomenclature are discussed.

# CHEMICAL CAUTERIZATION OF THE MUCOSA OF THE GALLBLADDER

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AND

C. FREMONT VALE, M.D.

DETROIT

Every surgeon occasionally finds it necessary to operate because of a diseased gallbladder when in his judgment something less than classic cholecystectomy is indicated. There are two types of patients in whose cases the decision to perform a less severe operation is important. These are: (1) persons whose general condition make the risk of cholecystectomy too great and (2) persons for whom removal of the gallbladder is hazardous because of the local lesion. In many clinics cholecystostomy is the operation performed in this group of patients; in others some form of partial cholecystectomy or cauterization is resorted to. Thorek<sup>1</sup> advised excision of most of the free portion of the wall of the gallbladder and electrocoagulation of the part attached to the liver. During the years 1935 to 1940 we have used cauterization of the mucosa of the gallbladder with solutions of phenol and alcohol, the procedure often called chemical cholecystectomy, as a preferred method for those patients in whom cholecystectomy seemed unwise. We have done this in the hope that it would prove more successful than cholecystostomy which in our experience is so often followed by a recurrence of symptoms and pathologic changes similar to those originally present.

The application of chemicals to the mucosa of the gallbladder in an attempt to destroy it is not new. As early as 1921 and again in 1926, Martin<sup>2</sup> presented a total of 7 cases in which acute cholecystitis in poor surgical risks was treated with incision of the gallbladder from the fundus to the cystic duct and application of iodine followed by drainage. He was convinced that this procedure absolutely destroyed

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From the Department of Surgery, Wayne University College of Medicine, and City of Detroit Receiving Hospital.

1. Thorek, M.: *Modern Surgical Technic*, Philadelphia, J. B. Lippincott Company, 1938, vol. 3, pp. 1580-1597.

2. (a) Martin, E. D.: *Cholecystostomy vs. Cholecystectomy*, New Orleans M. & S. J. **74**:4 (July) 1921; (b) *Complete Cholecystostomy vs. Cholecystectomy in Cases of Empyema of Gall Bladder*, South. M. J. **19**:198 (March) 1926.

the gallbladder. Likewise, Thompson, discussing Martin's second paper,<sup>2b</sup> stated: "The mucous membrane probably sloughs out during convalescence." Apparently these patients were cured at least for the follow-up period.

In 1928 Pribram<sup>3</sup> described mucoclasia, the procedure being similar to that of chemical cholecystectomy.

In 1927 Gatch<sup>4</sup> first mentioned chemical cholecystectomy. In 1930 he<sup>5</sup> reported 54 cases in which this treatment was used. Fifteen of these were cases of gangrenous cholecystitis. There was 1 death; apparently there was no recurrence of symptoms in the other cases. He was convinced of the ease with which the operation could be done in the presence of acute inflammation and the small risk to the patient. The indications included: (1) gangrenous cholecystitis; (2) a gallbladder densely adherent to surrounding structures; (3) broad attachment of the gallbladder to the liver; (4) a patient who is a poor risk. Our experience with the procedure described by Gatch for the period 1935 to 1940 is reviewed. We have studied also the effects of chemical cauterization of the mucosa of the gallbladder in dogs and in swine.

The technic we have used is similar to that described by Gatch. The fundus of the gallbladder is opened; the bile is aspirated, and any stones present are removed. Usually a portion of the free edge of the gallbladder is then excised, and the remainder of the mucosa of the gallbladder is treated with from four to six applications of 95 per cent solution of phenol each of which is followed by an application of 95 per cent solution of alcohol and drying with a sponge. No attempt is made to block the cystic duct. The phenol and the alcohol are allowed to gravitate well into the ampulla of the gallbladder. A soft rubber tube is inserted down to the ampulla, and the remnant of the gallbladder is folded and sutured about this tube which emerges through the fundus and is allowed to drain for eight to ten days. No further drainage of the abdominal cavity is done. This technic does not alter any procedure which might be necessary on the common duct or any other intra-abdominal viscus.

During the past five years we have had occasion to perform this operation in 47 cases. In general we were pleased with the smooth convalescence of the patients in spite of the acute process found at

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3. Pribram, B. O.: Treatment of Gall Bladder by Mucoclasia, *Med. Klin.* **24**:1147, 1927-1928.

4. Gatch, W. D., in discussion on Bruggeman, H. O.: Treatment of Acute Cholecystitis, *Tr. West. S. A.* (1927) **37**:345, 1928.

5. Gatch, W. D.: Chemical Cholecystectomy, *Tr. South. S. A.* (1929) **42**:110, 1930.

operation. Elderly people tolerated it especially well. In no case did a fistula persist.

In 6 of the 47 cases mentioned the operation was combined with exploration of the common duct.

Four (8 per cent) of the 47 patients died in the hospital. Of these 4, 3 were poor risks with an acute process. The fourth had a gastric resection in addition and died from a complication of that operation.

As we approached the end of the five year period and these patients were doing well clinically, it seemed that the mucosa of the gallbladder

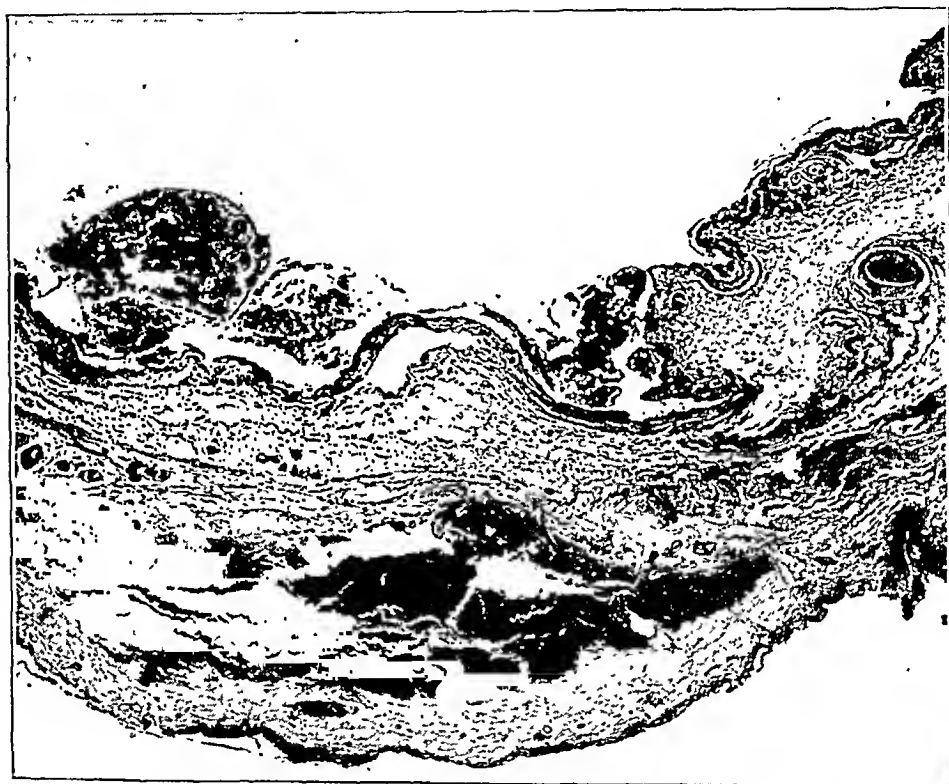


Fig. 1.—Photomicrograph of the wall of a dog's gallbladder two weeks after cauterization with phenol and alcohol, showing apparently complete necrosis of all coats.

must certainly be completely destroyed by this procedure. It was only when postoperative Graham-Cole examinations began to show visualization of the gallbladder that we decided to investigate more thoroughly.

In a follow-up of the remaining 42 patients we were able to make contact with 34. The average time since operation amounted to a little less than four years. Of these 34 patients, 29 (85 per cent) stated that they had had no recurrence of symptoms similar to those which

they had previous to operation and that there was no new symptom which related to the gallbladder. These were classed as good results. Three other patients stated that they remained free from symptoms if they were careful of their diet. However, they were troubled especially by greasy foods, cabbage and onions. These patients thought that they were improved since operation but that the result was not entirely good. They amounted to 8.8 per cent of the patients followed. There were 2 patients, or 6.2 per cent, who reported their condition as about the same. One of these, later operated on again, was admitted two years

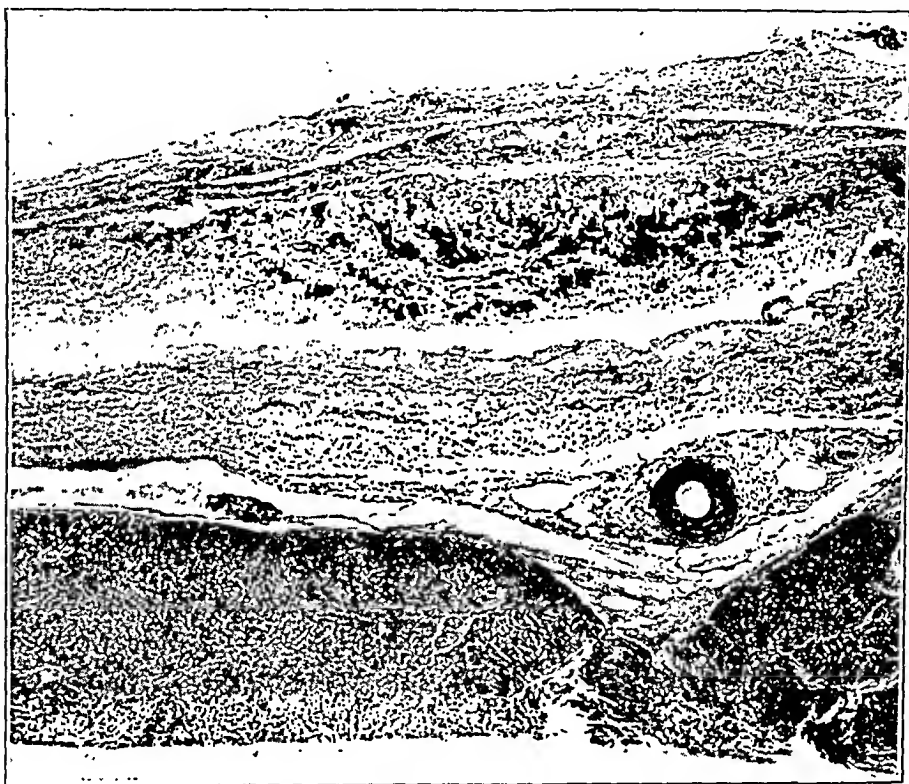


Fig. 2.—Photomicrograph of the wall of a dog's gallbladder fourteen weeks after cauterization with phenol and alcohol, showing well defined organization of the wall and disappearance of necrotic debris.

after chemical cholecystectomy with only mild pain in the right upper quadrant of the abdomen without evidence of an acute process. A Graham-Cole test did not show a functioning gallbladder. Reoperation revealed part of the omentum adherent to the liver and the bed of the gallbladder. Dissection disclosed a remnant of gallbladder  $1\frac{1}{4}$  inches (3.2 cm.) long with a lumen of  $\frac{1}{2}$  inch (1.27 cm.). The mucosa was

grossly atrophic. No stones were present. Microscopic examination (fig. 7) showed complete regeneration of both glandular and surface epithelium.

Of the 34 patients with whom contact was made, 18 had Graham-Cole examinations from six months to four years after operation. Regardless of symptoms, the gallbladders of these 18 were visualized

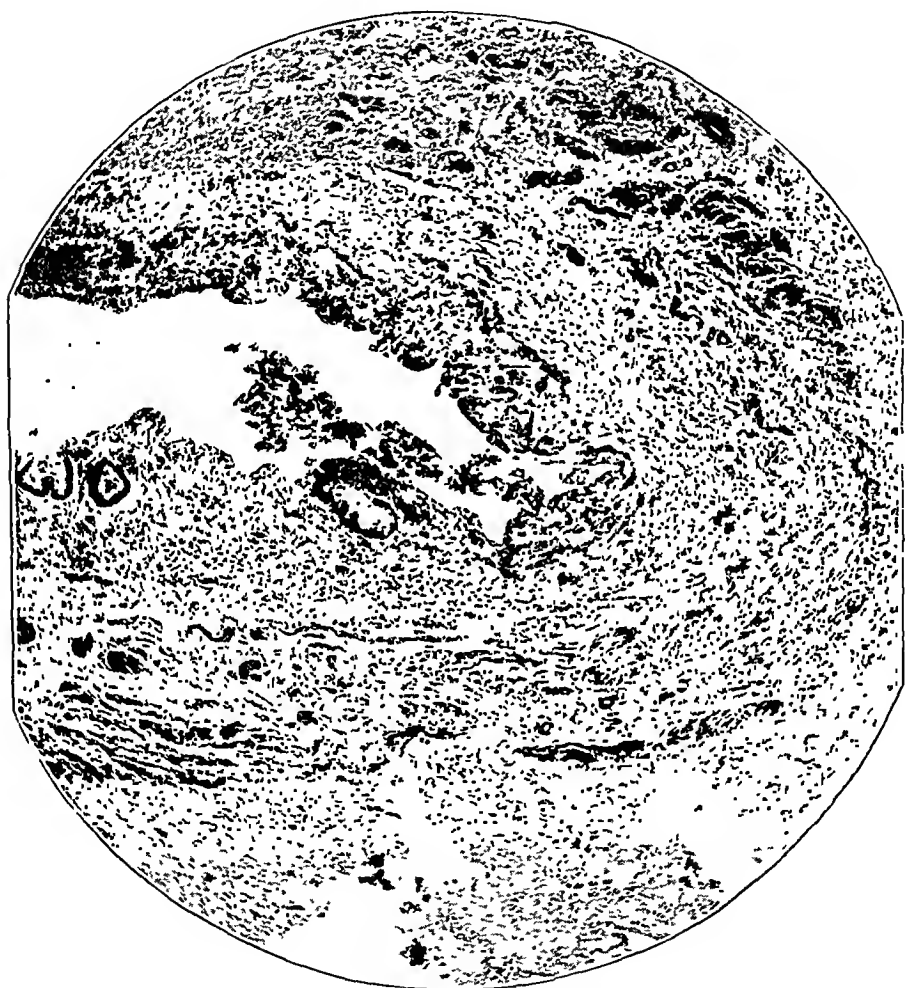


Fig. 3.—Photomicrograph of the wall of a dog's gallbladder six months after cauterization with phenol and alcohol, showing the structure. The picture suggests that the glands of Lushka develop first and the surface epithelium appears later, probably originating from glandular epithelium.

in varying concentrations of the dye in 7 (39 per cent). It is interesting to note that some of the gallbladders which did not function previous to operation were now visualized.

## EXPERIMENTAL STUDY

As reoperation is not common enough to allow a careful histologic study on human beings, animal experimentation has been substituted. The routine chemical cauterization as already described was carried out on both dogs and swine, with a total of 14 animals. Specimens were taken from the gallbladder before and just after cauterization with phenol and alcohol and at intervals from two to sixteen weeks in the dogs and from five weeks to eighteen months in the swine. At autopsy,

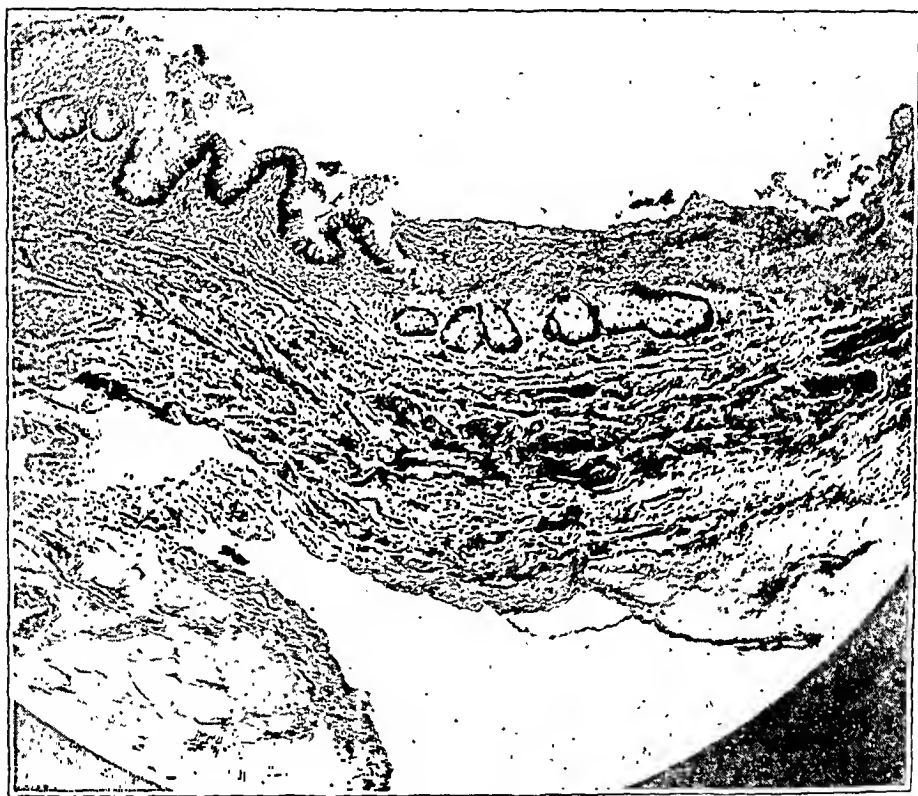


Fig. 4.—Photomicrograph of the wall of a dog's gallbladder nine months after cauterization with phenol and alcohol, indicating partial reconstruction of the mucosa. Some residual chronic inflammatory thickening of the wall is present.

in the majority of the animals the gallbladder was found to be extremely small but occasionally it approached normal size. Although hard to locate in some cases, a gallbladder lumen has always been present. In none of these have there been any stones or evidence of injury to the common duct or the liver.

In the many sections examined the picture was uniform, depending only on the length of the postoperative period. Immediately after

cauterization there was acute necrosis with apparently complete loss of epithelium and with congestion, edema and hemorrhage through the deeper layers. At the end of two or three weeks there was organization and occasionally formation of a small abscess in the wall. Often a few distended glands can be seen. By the tenth to the fourteenth week the epithelium was regenerated, although there was still infiltration of



Fig. 5.—Photomicrograph of a dog's gallbladder ten weeks after cauterization with Carnoy's solution. Apparently complete necrosis has taken place.

round cells and polymorphonuclear cells in the submucosa. At six to nine months the mucosa appeared fairly normal except for some fibrosis in the deeper layers (figs. 1, 2, 3 and 4).

In a further attempt to destroy the mucosa a similar procedure was carried out on the animals with the use of Carnoy's solution. This is



a strong cauterizing agent containing absolute alcohol, chloroform and glacial acetic acid and is used as a rapid fixative solution for pathologic specimens. According to this technic the abdomen is opened and the gallbladder isolated. A large caliber needle is inserted into the lumen of the gallbladder and the bile aspirated. The gallbladder is then irrigated with solution of sodium chloride until practically all the bile



Fig. 6.—Photomicrograph of a pig's gallbladder ten months after cauterization with Carnoy's solution. Development of glands is better than that of surface epithelium, which, however, is well regenerated.

has been removed. Enough Carnoy's solution is then instilled to fill the gallbladder, and this is allowed to remain until the serosa turns dark. This usually takes from three to four minutes. At the end of the time the Carnoy solution is aspirated. However, whatever remains on the wall of the gallbladder is not removed by irrigation.

The animals all survived this procedure, although at the time of operation the gallbladder was thoroughly fixed with the solution. Specimens of these gallbladders were taken ten weeks (fig. 5) to ten months later.

The reaction of the mucosa of the gallbladder following the procedure just described was much the same as that following the application of phenol and alcohol. Figure 6 shows a section from the gallbladder of a pig ten months after cauterization with Carnoy's solution. The mucosa was apparently fully regenerated. Some glands extended deep into the wall. There were a few areas of phagocytosed hemosiderin representing old hemorrhage.



Fig. 7.—Photomicrograph of a human gallbladder two years after cauterization with phenol and alcohol. The mucosa is fairly well restored.

#### SUMMARY

Chemical cholecystectomy has been carried out on 47 human beings, and the clinical results are reviewed.

Graham-Cole studies have been made postoperatively, and the results are shown.

Experimental cauterization has been carried out on animals both with phenol and alcohol and with Carnoy's solution, and the findings in these studies are given.

## CONCLUSIONS

In cases in which a less severe operation than removal of the gall-bladder is judged to be indicated, chemical cauterization of the mucosa is followed by a lower rate of recurrence of symptoms than cholecystostomy.

Despite extensive chemical cauterization, the mucosa of the gall-bladder regenerates rapidly. It appears that some of the deeper glands in the wall survive and become the source of new epithelium.

The term chemical cholecystectomy is a misnomer, because the gall-bladder is not completely eliminated as a functioning organ.

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# LYMPHOSARCOMA OF THE INTESTINE

## REPORT OF TWO CASES

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The relative rarity of tumors of the small intestine as compared with their frequency in the stomach and the large intestine is a common observation. It is further noted that the clinical manifestations of tumors in the stomach and the colon are more definite and readily recognized, while similar lesions in the small bowel are usually furtive and obscure, present variable and vague symptoms and even though suspected are found only by exploratory operations or at autopsy. This is true of lymphosarcoma, which, however, is one of the more common sarcomas of the gastrointestinal tract.

Although obscured by inaccurate terminology, certain well recognized types of sarcoma of the small bowel have been recorded. Speese,<sup>1</sup> in a summary of 99 different sarcomas of the small intestine, recorded the following types, in the order of their frequency; round cell sarcoma, 43; lymphosarcoma, 34; spindle cell sarcoma, 13; fibrosarcoma, 3; myxosarcoma, 2; myosarcoma, 2; mixed cell sarcoma, 1; melanotic sarcoma, 1.

It will be observed that the incorrect choice of terms used in pathologic diagnosis leaves the identity of types open to question. One must consider the possibility and the probability of lymphosarcoma and so-called round cell sarcoma being one and the same lesion.

## INCIDENCE

Baltzer<sup>2</sup> was unable to find a single instance of lymphosarcoma at the Berlin Pathologic Institute, Berlin, Germany, during the period 1859 to 1875. In 1900 Libman<sup>3</sup> noted 59 instances and commented on the

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1. Speese, J.: Sarcoma of the Small Intestine, *Ann. Surg.* **59**:727, 1914.

2. Baltzer, M.: Ueber primäre Dünndarmsarcome, *Arch. f. klin. Chir.* **44**:717, 1893.

3. Libman, E.: Sarcoma of the Small Intestine, *Am. J. M. Sc.* **120**:309, 1900.

infrequency of this tumor, pointing out that Smoler,<sup>4</sup> at the Pathologic Institute at Prague, Czechoslovakia, found only 13 cases of lymphosarcoma among 13,036 autopsies over a period of fifteen years. Nothnagel,<sup>5</sup> of Vienna, Austria, found only 12 instances of all varieties of intestinal sarcoma over a period of twelve years. Müller<sup>6</sup> was cited as observing only 1 instance of lymphosarcoma of the intestine in 102 cases of sarcoma of various kinds. Lecène<sup>7</sup> found enough additional cases to make the total of 89. Warthin<sup>8</sup> found only 2 lymphosarcomas of the intestine among 2,000 malignant neoplasms in young persons (1 to 30 years of age). Graves,<sup>9</sup> in a thorough search of the *Index Medicus* (encumbered by inaccurate terminology), concluded that there were 246 fairly authentic instances; to these he added 3, making a total of 249. Ulman<sup>10</sup> found 126 instances; these he added to the 249 reported by Graves to make a total of 375 instances of primary lymphosarcoma of the intestine. Cheever<sup>11</sup> recorded 16 verified instances of primary lymphosarcoma of the stomach and the intestine in a hospital of two hundred and forty beds over a period of nineteen years; during this time 976 patients entered with tumors of the stomach and the intestine. Of the 16 lymphosarcomas, 9 were in the stomach and 7 in the intestine. LaBree<sup>12</sup> reported a case of primary lymphosarcoma of the small intestine in a patient aged 51. This made approximately 376 cases of lymphosarcoma of the small intestine specifically recorded in the literature.

Our own experience with this type of tumor revealed only 1 among 38,076 surgical tissues and 11,446 autopsies. Another was encountered by one of us (D. G. M.) shortly after the first made its appearance. The unusual occurrence and the similarity in appearance and location as well as in the clinical manifestations seem to us to be worthy of record.

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4. Smoler, F.: Zur Kenntnis der primären Darmsarkoms, Prag. med. Wchnschr. **23**:135, 1898.

5. Nothnagel, H.: Die Erkrankungen des Darms und Peritoneum, Vienna, A. Hölder, 1898.

6. Müller, W.: Ueber Polyposis intestini mit besonderer Berücksichtigung des Röntgenbefundes, Beitr. z. klin. Chir. **119**:683, 1920.

7. Lecène, P.: Les tumeurs malignes primitives de l'intestin grêle: jéjunoniléon, Thesis, Paris, no. 196, 1904.

8. Warthin, A. S.: The Occurrence of Malignant Neoplasms in the Young, Arch. Int. Med. **15**:444 (March) 1915.

9. Graves, S.: Primary Lymphoblastoma of the Intestine, J. M. Research **40**:415, 1919.

10. Ulman, A., and Abeshouse, B. S.: Lymphosarcoma of the Small and Large Intestines, Ann. Surg. **95**:878, 1932.

11. Cheever, D.: Clinical Aspects and Treatment of Primary Lymphosarcoma of the Stomach and Intestines, Ann. Surg. **96**:911, 1932.

12. LaBree, R. H.: Small Bowel Tumors with Case Report of Lymphosarcoma of the Small Bowel, to be published.

## REPORT OF CASES

CASE 1.—R. E. H., a 42 year old married man, was first observed on May 21, 1938. He stated that ever since childhood he had had bilious attacks associated with nausea and vomiting. He complained of a tired feeling of a year's duration. Three months before consultation he began to have distress in the bowel, usually in the right side rather high up but sometimes also in the middle or even the lower part of the abdomen. The discomfort occurred several hours after meals and consisted of a dull ache which occasionally became a rather sharp uncomfortable pain. There was definite tenderness and increased resistance of the right side of the abdomen; occasionally an indefinite mass was felt. There were also a slight trace of sugar in the urine and some secondary anemia (hemoglobin



Fig 1 (case 1) —Roentgenogram (Dr. Dorwin Palmer) showing the character of the defect in the lower end of the ileum. Note the funnel-shaped obstruction and rarefaction at *I*.

content 94 per cent) The serologic test for syphilis gave a negative result. A roentgenogram revealed the terminal 8 inches (20 cm.) of the ileum to be somewhat dilated, giving evidence that a partial obstruction occurred distal to this area (fig. 1). The mucosa of the terminal portion of the ileum was mottled, suggesting an active inflammation. On the basis of these observations, it was believed that the patient had regional ileitis affecting the terminal portion of the ileum and producing partial obstruction. Surgical treatment was recommended.

The patient entered the hospital on May 24. He offered the additional information that he had suffered from chronic constipation, for which he took many laxatives over a long period. He also lost 5 or 6 pounds (2.3 to 2.7 Kg.).

The physical examination disclosed localized tenderness with increased muscular resistance in the right lower quadrant of the abdomen. On May 27 the abdomen

was opened through a right rectus incision. Some blood-stained fluid was found in the peritoneal cavity. There was also observed a mass occupying the terminal part of the ileum and the cecum, the lesion being confined chiefly to the last couple of inches of the ileum and the region of the valve. A rosette-like excrescence the size of a silver quarter projected from the anterior surface of the cecum. It was smooth but had a lobulated appearance and a deep reddish color. A portion was removed for biopsy. A few moderately large discrete soft nodes were found in the mesentery. The subserosal vessels were tortuous, dilated and filled. There

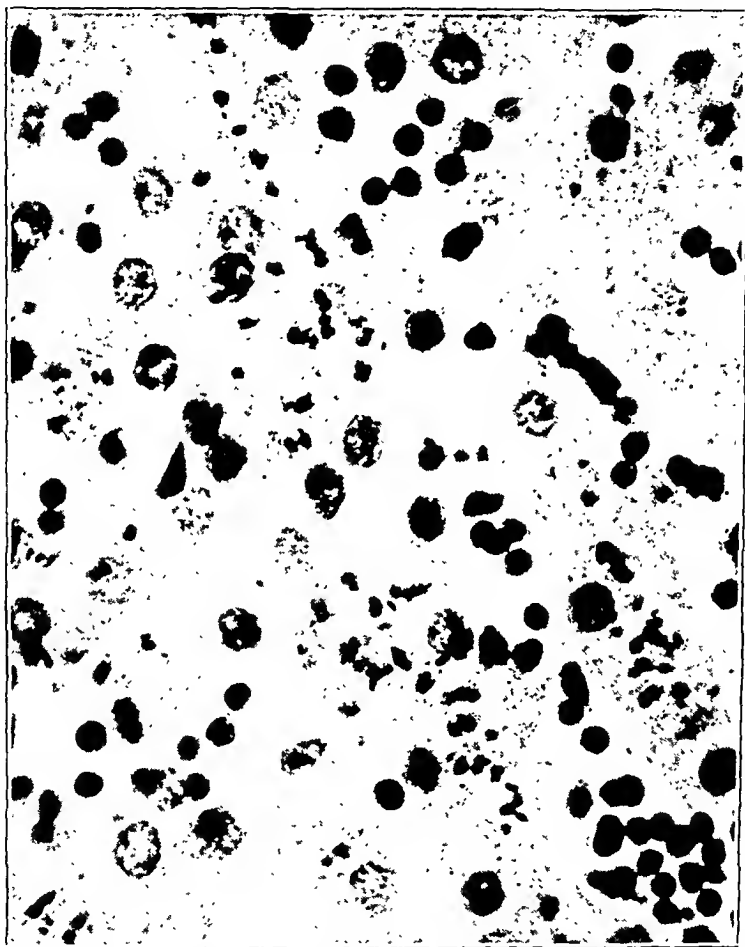


Fig. 2 (case 1).—Photomicrograph illustrating the lymphoblastic or reticulum-like character of the cells of the tumor.

were considerable contraction and apparent scarring of the cecum. The small intestine proximal to the involved area was not markedly distended. The ileum was cut 7 inches (18 cm.) from the ileocecal valve, and the proximal end was then anastomosed to the transverse colon in an isoperistaltic direction. The patient's condition did not warrant complete removal at that time. After the operation the patient's temperature was elevated to 101 F. at times during a period of about ten days, after which it returned to normal.

A restorative regimen with two blood transfusions was carried out. On June 17 the patient was returned to the surgical service (Dr. George Pfeiffer). The loop of the ileum was found plastered against the closed-off terminal portion of the ileum.

There was noted a small abscess between several of the loops of bowel, and perforation had occurred into the attached loop of the ileum. Three other tumor excrescences were seen projecting from the cecal wall. All were similar to the one first partially removed for biopsy. The ileocolostomy opening was found intact. Because of the adhesions and the perforation, the entire mass, consisting of the terminal part of the ileum, the cecum and a portion of the ascending colon, was removed, as was also the remainder of the ascending colon, including the hepatic flexure and the site of the recent ileocolostomy. The ends of the uninvolved parts of the ileum and the colon were then sutured together for a distance of



Fig. 3 (case 1).—Photograph showing one of the surfaces made by sectioning the lower end of the ileum and the cecum. C, cecum; I.V., ileocecal valve; T, tumor; I., ileum.

several inches, and both ends were brought out of the upper end of the incision. The patient was given 500 cc. of citrated blood at this time and a similar transfusion five days later. On August 26 the ileocolostomy opening was established. Because of chronic spasms the anal sphincters were also dilated at this time.

Gross examination of the first tissue removed for diagnosis revealed it to be rather firm, rubbery, somewhat lobulated, 3 cm. in length, 2 cm. in width and 1.5 cm. in thickness. Externally it had a glistening gray-tannish appearance, but on section it was uniformly gray to grayish white, except for small punctate brown knobs, presumably hemorrhages.



Microscopic examination revealed the following picture: There was an atypical capsular inclusion, presumably thickened peritoneal covering. The cellular tissue beneath this was of a peculiar type. The cells were monomorphic and variable in size, closely apposed to one another and having vesicular ovoid nuclei. The nuclei occasionally contained single nucleoli. Condensations of chromatin in the periphery of the nuclei could be seen. Mitotic figures were numerous. There were no so-called Hodgkin, or Sternberg-Reed, cells or eosinophils present. The cells were distinctly lymphoid, largely of the reticulum type. Mature lymphocytes were sparse. At one point within the so-called capsule there were two discrete nests of tumor cells. These appeared to lie within the capillaries or the lymphatics (fig. 2).

The pathologic diagnosis was highly malignant lymphosarcoma.

At gross examination of the tissue removed later (June 17) there were several specimens. One consisted of 12 cm. of the terminal part of the ileum and the attached appendix. Located 3 cm. proximal to the ileocecal valve was a relatively large annular slightly fungated tumor mass that encircled the lumen and the wall of the entire bowel. It lay largely in the angle between the ileum and the cecum and measured 7 cm. in length (fig. 3). In certain areas it was seen to have invaded the muscularis through to the subserosa. Here considerable hemorrhagic indurated inflammatory tissue was found on the external surface of the bowel. Sectioning portions of the tumor disclosed uniformly white homogeneous surfaces in which no hyperemia or visible necrosis was apparent. The other tissue consisted of 12 cm. of ascending colon and a small loop of small intestine that was anastomosed to the colon. About the anastomosis there was considerable kinking of the small bowel with some acute and chronic regional peritonitis.

Microscopic study of sections of the primary growth present in the terminal part of the ileum showed it to consist of cells similar in all respects to those described in the report of the previous biopsy.

The pathologic diagnosis was primary lymphosarcoma of the terminal part of the ileum, polypoid prolapse of ileac mucosa, hyperplasia of the mesenteric lymph nodes and healed ileocolostomy wound.

The patient left the hospital in good condition on October 26, after one hundred and fifty-five days of hospitalization. He returned to the tumor clinic one month later for further consideration of his treatment. The radiologist considered that roentgen therapy would be more injurious to the intestinal mucosa and surrounding tissues than it would be beneficial in destroying any portion of the possibly remaining tumor.

The patient was kept under periodic observation. There was apparent restoration of health (39 pounds [17.7 Kg.] gain in weight while he was at work). At the time of writing, four years after operative removal, there is still no evidence of recurrence.

CASE 2.—J. D., a 17 year old white male high school student, entered St. Luke's Hospital, San Francisco, on Dec. 12, 1938. His chief complaint was flatus and constipation. Three weeks prior to admission flatus with abdominal distention and pain of a griping nature began to develop. This condition was associated with poor bowel movements of diminishing volume with complete cessation for three or four days following a meal of barium sulfate November 29. Six days later he had a good bowel movement free from blood or mucus. Two days after this the previous symptoms again developed; they terminated with nausea and vomiting the night before admission.

Physical examination disclosed a well nourished and well developed young man who appeared acutely ill. The abdomen was tympanitic, rigid and tender. There was also slight secondary anemia (hemoglobin content 93 per cent). All other findings were normal.

*Roentgen Examination.*—A flat plate roentgenogram of the abdomen showed several dilated loops in the midportion of the ileum. The cecum was distended with flatus. The radiologist concluded that there was no obstruction of the bowel in the ileocecal region. The patient's temperature fluctuated between 37.5 and 38.4 C. (99.5 to 101.12 F.), while the pulse rate varied between 105 and 125. Examination of the blood revealed leukocytosis, the white cell count being 12,000



Fig. 4 (case 2).—Photograph disclosing the site of the tumor projecting into the cecum (C). The ileocecal valve fold (I.C.V.) seems to overlie part of the tumor; the ileum (I) seems to project upward.

with 78 per cent polymorphonuclears, 1 per cent eosinophils and 20 per cent lymphocytes. The patient was operated on the day of admittance by Dr. G. D. Delprat. A large nodular tumor was found in the ileocecal valve. It projected into the cecum. Several large loose hyperemic and edematous lymph nodes were found in the mesoappendix. The cecum, the ascending colon and the terminal part of the ileum were brought out through the incision, which was closed down around the projecting bowel. All of this tissue was enclosed in a rubber glove. A catheter was put into the cecum through one of the fingers of the glove. On December 10, three days later, the projecting loop of the intestine was removed with the cautery. The patient became afebrile two days later. He remained

so for eighteen days, after which a transitory temperature of 102.0 F. occurred and continued for two days. He was discharged on Jan. 23, 1939, clinically improved.

Gross examination by one of us (D. G. M.) yielded the following data: The surgically removed tissue consisted of 12 cm. of the terminal part of the ileum and 14 cm. of the cecum and the ascending colon with the appendix attached. Over the external surface of all these structures there was an abundance of yellowish gray to red purulent material. There was present a new growth in the vicinity

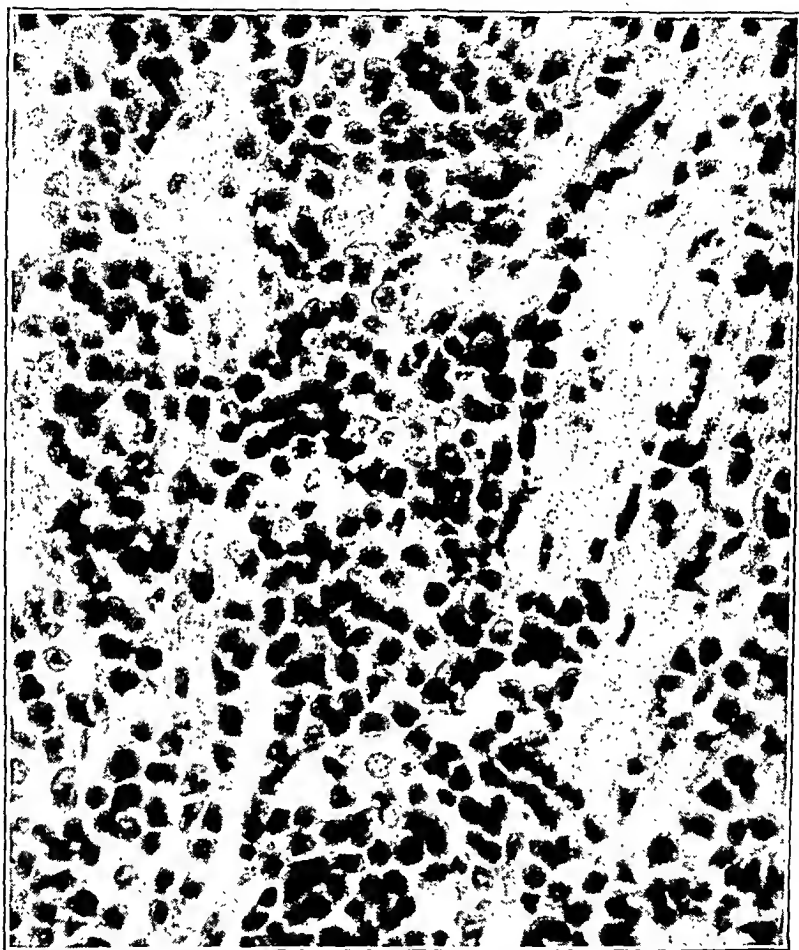


Fig. 5 (case 2).—Photomicrograph illustrating the uniform character of the cells as well as the invasion into the tissues.

of the ileocecal valve. The lumen at this point was narrowed but open. The growth was juxtaposed to the orifice and protruded into the lumen of the cecum, measuring 5 by 4 by 3.5 cm. in its various dimensions. The ileocecal valve was edematous. The mass was seen to lie in the distal portion of the ileum proximal to the valve. The mucous membrane was superficially slightly ulcerated. This area appeared to be an infarction in the tumor. At the angle formed by the ileum and the cecum there was a nest of enlarged firm, hard lymph nodes. On section of the tumor mass as well as of the lymph nodes there was observed a

uniform yellow-gray glistening white structure. The entire wall of the ileum at the site of the tumor appeared greatly thickened. The appendix was grossly unchanged (fig. 4).

Microscopic examination revealed an extremely cellular growth with numerous closely packed medium-sized lymphocytes all similar in appearance. All of these seemed to be mature lymphocytes, and mitotic figures in them were present in moderate numbers (fig. 5). In the area described as containing the infarct there was extensive necrosis. The blood vessels contained fibrin thrombi. The mucous membrane extending over the tumor seemed to be of the type in the large bowel or the colon. The lymphocytes seemed to invade the muscular layers as well as the serosa and to lie in dilated lymphatic spaces. All of the lymph nodes on examination revealed similar structure. In some portions of the section the cells appeared to be largely of the lymphoblast type.

The pathologic diagnosis was primary lymphosarcoma of the ileocecal valve.

Three weeks after discharge from the hospital, the patient began to have roentgen treatments as follows: January 30 to February 15, 1,600 r to the anterior lower portion of the abdomen with the use of a 0.13510 mm. tin filter, a 0.25 mm. copper filter and a 2.5 mm. aluminum filter. On March 20 he began a second series of treatments which were administered during a period from that date to April 10, 1,400 r to the anterior lower portion of the abdomen, 400 r to the anterior upper portion of the abdomen and 400 r to the lower portion of the abdomen posteriorly.

The patient continued to be nauseated and vomited at least once a day. On reentry to the hospital on April 10, he appeared weak and emaciated. The colostomy opening was functioning well. No other noteworthy changes had occurred, but he became progressively worse and died three days later. There was secondary anemia (hemoglobin content 62 per cent). The white blood cell count was 11,800 with 85 per cent polymorphonuclears and 5 per cent lymphocytes.

The autopsy by one of us (D. G. M.) disclosed the following pertinent conditions: recurrent metastatic lymphosarcoma involving the peritoneum, the heart, the anterior mediastinum, the mesentery and the retroperitoneal organs and tissues (the kidneys, the pancreas, the right psoas muscle and the periadrenal tissues); pulmonary atelectasis; emaciation; anemia, and hydronephrosis.

#### ETIOLOGY

The cause of these tumors, as of all tumors, is not definitely known. Lymphosarcoma of the intestine is most commonly found in male patients. The age incidence shows that the majority of instances occur in the third, fourth and fifth decades. In a group of 7 cases reported by Cheever, 4 of the patients were men and 3 were women; the average age was 53.5 years, the youngest patient being 30 and the oldest 75. The average range of ages given by him was 45 to 56. Thus it may be seen that the majority of these tumors come in the early tumor age period, although they may be found at any age. Ulman quoted Zwalenberg as observing one that developed six weeks after abdominal injury. Petersen<sup>13</sup> in a series of 85 cases found 3 in which the relation of the tumor

13. Petersen, E.: Sarcomas in Small Intestine, *Hospitaltid.* 66:782 and 797, 1923.

to injury seemed apparent. In a single instance reported by Schaaf,<sup>14</sup> a male high school student aged 15 years had epigastric distress following a contest in which he was an anchor man in a tug of war, during which he tied the rope around his waist, experiencing a constricting effect on his abdomen. Intussusception with a tumor was found in the ileum.

Primary inflammatory processes have been commented on as possibly causative. Libman found reference to tuberculosis in 1 instance, syphilis in another and protozoan infection in still another. Rankin<sup>15</sup> commented on the association in 2 instances of lymphosarcoma of the large intestine with chronic ulcerative colitis. Like other neoplasms, therefore, the exact initiating agent is unknown. Some focal overtaxation of lymphatic function seems apparent.

#### PATHOLOGY

The most common site of lymphosarcoma of the intestines is said to be the ileum. Of the growths of this type occurring in the large intestine, the largest number are found in the rectum. Krueger<sup>16</sup> reported 37 cases, in 16 of which the tumor was in the ileum and in an equal number in the rectum. Speese collected 42 cases with the growths distributed as follows: 15 in the duodenum, 18 in the jejunum, 2 in the jejunoileum and 14 in the ileum. Ulman found the ileum involved in 48 cases among 126 authentic cases of lymphosarcoma of the small and large intestines. The majority of the lymphosarcomas of the small intestine are not unusually large. The tumor reported by Benjamin and Christopher<sup>17</sup> measured 4 by 4.5 by 4 cm. Lymphosarcomas have a tendency to lobulate and to grow expansively in the wall of the bowel. We agree with Cheever, who pointed out that they probably begin in a nidus of lymphoid tissue, such as a follicle in the submucosa, and then spread characteristically by obliterating the wall of the bowel. It is agreed that these lymphosarcomas have a scanty and delicate reticulum, so that there is little tendency for them to contract and restrict the visceral lumen. The infiltrating lymphosarcomas do not, therefore, develop into massive pedunculated growths, as do carcinomas, with extension to the peritoneal or visceral cavities. Ulcerations, so characteristic of carcinoma, occur late. Metastases, either regional or general, may occur by the blood or lymph stream. The regional metastases may be so striking as to overshadow the primary tumor growth. Cheever expressed the opinion that

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14. Schaaf, R., and Kraemer, M.: Lymphosarcoma of the Ileocecal Valve, *Rev. Gastroenterol.* **7**:248, 1940.

15. Rankin, F. W., and Chumley, C. L.: Lymphosarcoma of the Colon and Rectum, *Minnesota Med.* **12**:247, 1929.

16. Krueger, F.: Die primären Bindegewebsgeschwülste des Magendarmkanals, *Inaug. Dissert.*, Berlin, C. Vogt, 1894.

17. Benjamin, E. L., and Christopher, F.: Primary Lymphosarcoma of the Small Intestine, *Am. J. Clin. Path.* **10**:408, 1940.

the primary invasion of lymph nodes is by direct permeation rather than by free-cell metastasis. In 1 of the instances reported here the extension was apparently only through the wall of the bowel, while in the other the lymph nodes were seemingly involved. It is significant that the course seemed much more rapid in the younger person (case 2) although the cell type (mature lymphocyte) was seemingly less malignant. While both of these tumors seemed to occur in the lower end of the ileum, 1 (case 2) seemed to have more definitely developed in the ileocecal fold.

#### SYMPTOMATOLOGY

The signs and the symptoms of lymphosarcoma of the small intestine are dependent on their location, duration and extent. In the 2 instances here reported, the symptoms were somewhat similar except for intensity. One patient (case 1) complained of some indefinite long-standing disturbance in the bowel, having had a history of nausea, vomiting and bilious attacks in childhood and later constipation requiring excessive use of cathartics. The other patient's (case 2) complaints were less definite, but constipation was noted. In both atypical symptoms of incomplete obstruction, with tenderness, pain, tympanites, nausea and vomiting, finally developed. In case 1 the clinical impression was that the condition was regional enteritis; in case 2, that it was intestinal obstruction.

Speese pointed out that the symptoms may be slight at the onset with later associated pain, loss of appetite, nausea, vomiting, irregularity of the bowels, distention of the abdomen and possible palpable tumor. He classified lymphosarcomas of the small intestine as follows: (1) latent tumors, discovered by autopsy; (2) tumors with general manifestations, distention of the abdomen or presence of a mass being first noted; (3) tumors the first symptoms of which are due to intussusception or other intestinal obstruction or to perforation; (4) tumors with manifestations resembling those of tuberculous peritonitis; (5) tumors of which jaundice is the first symptom; (6) tumors resembling ovarian cysts; (7) tumors simulating appendicitis.<sup>18</sup> Symptoms vary in duration from three weeks to seventeen months with an average of six and a half months.<sup>11</sup> The chief complaints are abdominal pain, vomiting, constipation and loss of weight. Bloody or tarry stool was found in only 1 case. In many instances the tumor can be felt. Roentgen examination generally reveals residuum in the loops of the ileum, rigidity of the ileocecal valve, a filling defect of the cecum and distention and obstruction of the small intestine. Visible peristalsis and vomiting after meals may occur when a lympho-

18. Booth, cited by Goldstein. Goldstein, H. I.: Primary Sarcoma of the Intestines, *Am. J. Surg.* **35**:240 and 323, 1921; Primary Sarcoma of Appendix: Lymphosarcoma of Appendix with Acute Intestinal Obstruction in a Young Woman, *Am. J. M. Sc.* **161**:870, 1921. Hagyard, C. E.: Lymphosarcoma of the Appendix and Caecum, *Northwest Med.* **24**:342, 1925.

sarcoma is located in the upper part of the small bowel (Benjamin and Christopher). As Libman pointed out, partial stenosis with dilatation is one of the common characteristics. Lymphosarcoma of the intestine is insidious in its development and much more difficult to recognize than carcinoma.

Early diagnosis with complete and radical removal offers the only hope in a case of lymphosarcoma of the intestine, with which at best the prognosis is usually grave.

#### SUMMARY

Two cases of primary lymphosarcoma of the lower end of the small intestine are presented.

In one the clinical diagnosis was regional ileitis; in the other, intestinal obstruction, cause unknown. One patient (case 1) is still well three years after operation; the other (case 2) died four months after operation with general metastases.

Lymphosarcoma of the small intestine is relatively uncommon, there being approximately 376 authentic instances. In our own experience there was 1 case among 38,076 surgical tissues and 11,446 autopsies.

Although the prognosis is poor, early recognition and complete surgical removal offer the best chance.

The infrequency of lymphosarcoma of the small intestine has the same basis as does that of other tumors in this location, namely, the anatomic and functional character of the small bowel.

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# STAB WOUND OF THE PULMONARY ARTERY WITH SUTURE AND RECOVERY

REPORT OF A CASE WITH A BRIEF REVIEW OF TRAUMATIC  
CARDIAC SURGERY

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Although suture of stab wounds of the heart is a relatively recently developed surgical procedure, some 345 cases have been reported in the literature with recovery in approximately 60 per cent. Elkin<sup>1</sup> estimated this rate to be somewhat too high, because numerous isolated cases in which treatment is unsuccessful are never reported. He therefore places the recovery percentage at no greater than 50 per cent, even at the present time.

In a careful search of the literature one finds that not only are instances of stab wounds of the intrapericardial portion of the pulmonary artery rare but the mortality rate has been 100 per cent. It is of considerable interest, then, to report a case of stab wound of the pulmonary artery with operation and complete recovery.

Excellent reviews of the history of heart wounds have been presented by Elkin, Bigger,<sup>2</sup> Peck,<sup>3</sup> Pool,<sup>4</sup> Glasser and associates,<sup>5</sup> and reference to their articles is suggested for a complete survey. Let it suffice here to say that the injury has long been recognized but that even the great Billroth<sup>6</sup> wrote that any attempt to treat such a wound operatively was not only prostitution of surgery but also madness. Rehn<sup>7</sup> is credited with the first successful suture of the human heart in 1896.

As with most operative conditions there has been a gradual decrease in the mortality rate with added experience through the years.

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From the Department of Surgery, Duke University School of Medicine.

1. Elkin, D. C.: The Diagnosis and Treatment of Cardiac Trauma, *Ann. Surg.* **114**:169, 1941.

2. Bigger, I. A.: Wounds of the Heart and Pericardium, *South. M. J.* **25**: 785, 1932.

3. Peck, C. H.: The Operative Treatment of Heart Wounds, *Ann. Surg.* **50**:101, 1909.

4. Pool, E. H.: The Treatment of Heart Wounds, *Ann. Surg.* **55**:485, 1912.

5. Glasser, S. T.; Mersheimer, W., and Shiner, I.: Bullet Wound of Left Cardiac Auricle with Suture and Recovery, *Am. J. Surg.* **53**:131, 1941.

6. Billroth, cited by Ricketts, B. M.: *Surgery of the Heart and Lungs*, New York, Grafton Press, 1904.

7. Rehn, L.: Ueber penitrierende Herzwunde und Herznaht, *Arch. f. klin. Chir.* **55**:315, 1897.



In 1909 Peck listed 160 cases to date in which treatment was by operation; the mortality rate was 63.13 per cent.

In 1912 Pool added 77 cases with a mortality rate of 49 per cent.

In 1923 Smith<sup>8</sup> collected 49 additional cases with a mortality rate of 36 per cent.

Bigger collected 70 cases in 1933 with a mortality rate of 30 per cent, and in 1941 Elkin published 38 cases of his own or of his staff with a mortality rate of 42 per cent. Elkin and Bigger<sup>9</sup> reported the only cases of injury to the pulmonary artery intrapericardially. Each had 1 case. In 1 case death ensued during an attempted aspiration to relieve cardiac tamponade, and in the other case the patient died two days postoperatively. No autopsy was obtained, but clinically the patient had overwhelming pneumonia.

The chief causes of postoperative death have been listed by Bigger as infection, pulmonary infarction and recurring cardiac tamponade. The last might occur from insufficient closure of the heart wound and has led many to advise pericardial drainage for a few days. Pool, Bigger and Elkin advised against this, however, as being a possible cause of cardiopericardial adhesions and of infection. Instead, all advised closure of the pericardium with widely spaced sutures and possibly a small drain down to the pericardium.

#### MECHANISM OF INJURY AND PATHOLOGIC FUNCTION

The most common cause of injury in all cases reported has been a stab with a knife or an ice pick. Gunshot wounds rank next but apparently usually cause almost instantaneous death. Occasional glass splinters and similar shattered fragments are introduced by mechanical accidents. The majority of wounds, however, are inflicted with either suicidal or homicidal intent.

As soon as injury to the heart occurs, bleeding into the pericardial sac takes place. Since this is an inelastic structure and since the wound of entrance into it usually is rapidly plugged by the overlying muscle, the tension within the sac rises. This restricts the muscular activity of the heart, and since the tension rapidly rises above the pressure within the vena cava, it prevents the filling of the right auricle. The cardiac intake is diminished; cardiac output falls, and cerebral anemia rapidly produces death. This is known as death from cardiac tamponade, as the actual loss of blood is usually inconsequential.

A priori, then, the symptoms of this injury, must be: (a) distention of the veins of the neck with a high venous pressure; (b) a diminishing

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8. Smith, W. R.: *Cardiorrhaphy in Acute Injuries*, Ann. Surg. **78**:696, 1923.

9. Bigger, I. A.: *The Diagnosis and Treatment of Heart Wounds with a Summary of Twenty-Five Cases*, South. M. J. **33**:6, 1940.

blood pressure with a rapidly disappearing pulse pressure; (c) irregularity of the cardiac rate and rhythm, and (d) unconsciousness with either stupor or wild delirium.

#### DIAGNOSIS

It is evident from Elkin's, Bigger's and Shipley's<sup>10</sup> experiences that the number of cases of cardiac wounds diagnosed varies with the degree of suspicion and care in examination.

The history, if obtainable, is usually that of freedom from symptoms for a few minutes. My patient was brought to the hospital by a friend and walked with some support. Others have walked or run a city block or more. Exhaustion soon follows. The position of the chest injury and the direction of the blow or shot if known assists in the diagnosis.

The patient shows all the signs of shock. Venous pressure may be taken by inserting a needle directly into a neck vein. It is frequently above 200 to 300 mm. of water. The heart sounds are weak and muffled. Cardiac dulness is enlarged. Pulse pressure is low. Fluoroscopy shows a quiet heart. Electrocardiograms are of no value and are contraindicated because of the unnecessary delay involved in obtaining them. Hesse,<sup>11</sup> Borchardt<sup>12</sup> and others have advised exploration when the diagnosis is probable but not positive. Typical cardiac tamponade was present in only 11 of 21 cases of Hesse, and hemothorax may complicate the diagnosis.

#### TREATMENT

In 1868 Fischer<sup>13</sup> collected 452 cases of heart injury. In all of these treatment was nonoperative; 10 per cent recovered. During the past ten years the average percentage of recovery in the cases reported (about 80 in all) has been 64 to 71 per cent.

The answer, then, is obvious. Moreover, as Rehn pointed out in 1896, a heart wound which has healed without surgical intervention leaves a weak scar which may rupture or become the site of an aneurysm. In 1899 Loison<sup>14</sup> collected 9 such cases. On the other hand, Le Fort and Decoulx<sup>15</sup> examined 55 cases twenty years after original injury

10. Dr. A. M. Shipley presented his experience in a clinic on wounds of the heart at Duke University School of Medicine, Dec. 10, 1940.

11. Hesse, E.: Ein Fall von 26 jährigen Bauerresultat einer Herznaht nach Schussverletzung, *Zentralbl. f. Chir.* 62:1874, 1935.

12. Borchardt, M.: Ueber Herzwunden und ihre Behandlung; Pfählungsverletzung von Herz und Lunge, *Samml. klin. Vortr.*, 1906 (Chir. nos. 113-114), pp. 297-350.

13. Fischer, G.: Die Wunden des Herzens und des Herzbeutels, *Arch. f. klin. Chir.* 9:571, 1868.

14. Loison: Des blessures du pericarde et du coeur et de leur traitement, *Rev. de chir.* 19:774, 1899.

15. Le Fort, R., and Decoulx, P.: Bullets in the Heart and Mediastinum: Late Results in Fifty-Five Cases After More Than Twenty Years, *J. de chir.* 52:1, 1938.

and obtained electrocardiograms in 16. These were all normal. Elkin stated that in his 22 successful cases there have been no residual symptoms.

#### TECHNIC

Various incisions have been advised, the principal ones being median sternotomy,<sup>16</sup> intercostochondral thoracotomy,<sup>17</sup> quadrangular flap<sup>18</sup> and the transverse incision of Elkin. In my case a left parasternal incision with a lateral flap after the manner of Meyer<sup>19</sup> and Nystrom<sup>20</sup> for removal of pulmonary embolus was used. This proved to be ideal under the circumstances.

Elkin noted that it is easier to separate rib from pleura than cartilage from pleura and therefore advised cutting the rib laterally; then by elevating the rib cartilage, one can remove it at the sternal junction. Usually the internal mammary artery has to be divided and ligated.

When the pericardial sac is opened, a search is made for the wound. This is closed with either catgut or silk interrupted sutures, the finger being placed over the wound and not into it, since the heart muscle is extremely friable. Beck<sup>21</sup> advocated stabilization of the heart by traction sutures through the apex. Pericardial blood is removed by suction, and the cavity is irrigated with physiologic solution of sodium chloride. Closure of the pericardium should not be too tight, as accumulation of serum and blood may reproduce the cardiac tamponade. If heart action ceases, release of tension, gentle massage and direct introduction of epinephrine will usually restore contraction.

The blood aspirated from the pericardial cavity may be citrated and reintroduced into the blood stream as an autotransfusion. Blood or plasma from a blood bank will be found helpful immediately post-operatively.

Local anesthesia is thought by some to be sufficient. Occasionally a patient has been so unconscious as not to require any anesthesia at all. Many patients are intoxicated or wildly delirious, and general anesthesia is necessary to control them. Elkin expressed a preference for positive pressure inhalation anesthesia, which permits control of

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16. Duval, P., and Baudet, R.: Sur une observations de plaie penetrante du ventricule droit traitee par la suture, *Bull. et mém. Soc. d. chirurgiens de Paris* **33**:15, 1907.

17. Spangaro, S.: Sulli tecnica da seguire negli interventi chirurgici par ferite del cuore e su di un nuovo processo di toracotomia; *Clin. chir.* **14**:227, 1906.

18. Fontan, J.: Plaie du coeur; suture du ventricule gauche; guérison, *Bull. et mém. Soc. d. chirurgiens de Paris* **27**:1099, 1901.

19. Meyer, A. W.: A New Technic for Successful Surgical Treatment of Pulmonary Embolism, *Deutsche Ztschr. f. Chir.* **231**:586, 1931.

20. Nystrom, G.: Experiences with the Trendelenburg Operation for Pulmonary Embolism, *Ann. Surg.* **92**:498, 1930.

21. Beck, C. S.: Wounds of the Heart, *Arch. Surg.* **13**:205 (Aug.) 1926.

accidental opening of the pleura. Bigger preferred local anesthesia, while Vakhamreev<sup>22</sup> used ether entirely. Since my patient was intoxicated, it was feared he would be difficult to control after release of the tamponade. Ether was the only general anesthetic available at the time of his injury and was therefore used.

#### POSTOPERATIVE COMPLICATIONS

Infection is the most common cause of postoperative death, with pneumonia and recurrent cardiac tamponade following. For this reason, although haste is usually necessary, scrupulous sterilization of skin and instruments and customary aseptic technic are imperative. An oxygen tent is of assistance postoperatively. Heparinization might be advisable to prevent intra-auricular and intraventricular clots with resultant embolus and infarcts. Thorough debridement or excision of the original wound tract should be carried out. Tetanus antitoxin or toxoid should be administered.

Occasional deaths have been due to tension pneumothorax. Careful frequent examination of the chest is essential to detect this as well as incipient pneumonia and empyema.

#### REPORT OF CASE

J. B., a 42 year old Negro man, was admitted to Lincoln Hospital on Oct. 13, 1940, about twenty minutes after having been stabbed in the left side of the chest anteriorly with an ice pick. Respirations were grunting. The patient denied any severe pain but complained of soreness and pressure within his chest.

Examination showed temperature 97.4 F., pulse rate irregular (counted by one nurse as 10 per minute, but 55 when I saw the patient a few minutes later) and respiration rate 8. Blood pressure was 80 systolic and 62 diastolic. Immediate fluoroscopy showed a large boot-shaped practically pulseless heart shadow. The general physical examination revealed no abnormalities except a small puncture wound in the third interspace just to the left of the sternum which was not bleeding. During the time interval necessary to communicate with the service physician, Dr. J. W. V. Cordice (who gave me the opportunity of operating on this patient), and to set up the operating room, his blood pressure fell to 70 systolic and 58 diastolic and then to 60 systolic and 54 diastolic; the pulse pressure was only 6 mm. of mercury. The pulse rate remained around 60. He was cold with a clammy skin and was perspiring freely. Temperature forty-five minutes after admission and just before operation was 94.6 F. He was given 0.5 cc. of coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) immediately before anesthesia, and the blood pressure rose to 80 systolic and 66 diastolic.

With the patient under anesthesia induced with ether, an incision about 8 cm. long was made parallel to the left side of the sternum from the third rib to the fifth. This was converted to a T incision by adding a short lateral incision in the third interspace. The muscle was cut through and the rib exposed. The

22. Vakhamreev, P. I.: Heart Injuries Observed in Seven Cases, *Vestnik khir.* 52:182, 1937.

cartilaginous portions of the fourth and fifth ribs were removed. (I believe that it would have been better to have removed the third instead of the fifth, as I had some difficulty in exposing the upper portion of the operative site.) The path of the stab wound could easily be followed by the amount of hemorrhage in the muscle surrounding it. After the cartilaginous portions of the ribs were removed, the internal mammary vein was slightly injured and had to be ligated, but the artery was not disturbed. There were a partial pneumothorax and a small hole in the pleura which was closed with a ligature. The pleura was then pushed laterally and upward; this exposed the pericardial sac which was tense and bluish. A small opening was made into the pericardium, and immediately there spurted upward a stream of dark blood. This was aspirated, and a total of about 400 cc. was removed. The heart action immediately improved both visibly and from the standpoint of the anesthetist, who reported the pulse as full and bounding. Inspection of the right auricle and the right ventricle showed no wound whatsoever. However, there was a small opening in the pulmonary artery, apparently about 1 cm. above the valves, from which, at each heartbeat, a stream of blood poured forth. With considerable difficulty, owing to the constant tearing of the sutures in this thin wall, the opening was closed. A purse string suture of double medium black silk was first used, and this was reenforced with several mattress sutures. The opening was about 4 to 5 mm. in diameter. The pericardium was then resutured with interrupted medium black silk sutures. The muscle was reapproximated with the same material, and the skin was closed with a layer of subcutaneous and a layer of superficial interrupted fine black silk. The patient returned to the ward in fair condition, his blood pressure being 90 systolic and 60 diastolic.

*Postoperative Course.*—The patient was given morphine sulfate and a continuous infusion of physiologic solution of sodium chloride immediately after the operation. Twelve hours later his blood pressure was 90 systolic and 60 diastolic and twenty-four hours after operation 100 systolic and 52 diastolic, and he felt fine. There were a few rales heard over the left lung field and some hyperresonance. It was felt that the pneumothorax had not entirely cleared up. On the following day fulminating bilateral bronchopneumonia with slight hemopneumothorax developed on the left. He was given blood transfusion and sulfathiazole (2-[*para*-aminobenzene-sulfonamido]-thiazole) in the usual doses. The response was excellent; the pneumonia subsided, and for a week he was afebrile. Then a daily elevation of temperature began again, and empyema was found to have developed on the left side. Trocar thoracotomy was performed with closed tidal drainage on November 11. The empyema finally cleared up, and the tube was removed on December 4. During part of this course there was mild infection of the chest wound, but this also healed. The patient was discharged from the hospital on December 10, sixty days after admission, with complete healing of both incisions and reexpansion of the lung, a normal heart shadow and some thickening of the pleura at the left base. Reexamination one year later showed him to be completely well at that time.

#### COMMENT

Venous pressure determination was not performed on this patient, as the physical signs and fluoroscopic examination pointed definitely to an intrapericardial wound. The most significant factor in establishing such a diagnosis was the rapidly diminishing pulse pressure, which was striking.

The pulmonary complications were not unexpected since the patient had partial pneumothorax with some hemothorax following penetration with a dirty weapon. In addition there was the trauma of a forty minute anesthesia induced with ether in a moderately intoxicated patient.

No transfusion or intravenous fluids were administered to this patient for forty-eight hours postoperatively so as not to augment any bleeding tendency by a rapid rise in blood pressure or cardiac output.

#### SUMMARY

A case of successful suture of a stab wound of the pulmonary artery is recorded. A short general discussion of the diagnosis and the treatment of perforating wounds of the heart is presented.

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## ARTERIAL BLOOD FLOW IN EXTREMITIES WITH VARICOSE VEINS

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AND

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CINCINNATI

In view of the frequent association of varicose veins of the extremities with trophic changes in the skin, it becomes important to ascertain the state of the circulation in the former condition. Using the same patient, de Takáts and his associates<sup>1</sup> compared the gaseous content of venous blood from a normal upper extremity with that from a lower extremity with varicose veins and found a uniform increase in carbon dioxide and a decrease in oxygen content in the sample obtained from the lower limb. A similar procedure in a group of normal subjects revealed no such difference, at least as far as carbon dioxide content was concerned. On the basis of these results, the authors concluded that the tissues of a leg with varicosities are in a state of chronic anoxemia. According to them, this factor together with the retention of carbon dioxide and other waste products is responsible for the various cutaneous complications frequently seen with this condition. Using the histamine flare test, these authors obtained results which they interpreted as indicating that patients with varicosities also have some interference with arterial blood flow, possibly as a result of arteriolar spasm.

Blalock,<sup>2</sup> on the other hand, noted that in patients with varicose veins of one of the lower extremities the oxygen content from the femoral or saphenous vein was higher on the diseased side. This difference between the normal and the abnormal extremity was more pronounced when ulceration was present. No definite relation appeared to exist, however, with respect to the oxygen content of blood from the dilated veins in the lower part of the leg and that of blood from similarly located vessels on the control, normal side. According to him,

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From the May Institute for Medical Research, the Jewish Hospital.

This study was aided by a grant from the Samuel and Regina Kuhn Fund.

1. de Takáts, G.; Quint, H.; Tillotson, B. I., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, *Arch. Surg.* **18**:671 (Feb.) 1929.

2. Blalock, A.: Oxygen Content of Blood in Patients with Varicose Veins, *Arch. Surg.* **19**:898 (Nov.) 1929.

the data suggested that the total flow of blood through a leg with varicose veins was increased. Holling and associates<sup>3</sup> confirmed Blalock's results in part by finding that the oxygen tension in the blood from the varicose saphenous vein was no lower than in that from the normal side.

Inasmuch as the procedure used in the investigations just cited serves only as an indirect measure of the rate of blood flow and since the results obtained by the different workers were for the most part contradictory, it was considered advisable to reinvestigate the subject by means of the venous occlusion plethysmographic method.

#### METHOD

The study was performed on a series of 13 subjects with varicosities of the lower extremities and 1 with sclerotic veins of the upper extremity; readings of blood flow in cubic centimeters per minute per hundred cubic centimeters of limb volume were obtained according to the technic previously described.<sup>4</sup> Patients with ulcers of the skin were not utilized (except 1 [M. C.]), since the venous occlusion plethysmographic method does not lend itself to the examination of open cutaneous lesions without the risk of aggravating the existing condition. In patients in whom the degree of involvement was practically the same in both lower extremities, only one lower extremity was studied; in other instances, in which the degree of involvement was different or in which only one side was affected, determinations were made on both legs simultaneously. In a number of patients the rate of flow in the normal forearm also was investigated. The temperature of the water in the plethysmograph was maintained at 32 C., and the temperature of the room varied between 25 and 27 C. After the subject had become accommodated to his environment, fifteen to twenty measurements of blood flow were obtained under resting conditions.

#### RESULTS

As controls for the results obtained in the present series of patients the readings of resting blood flow for a group of 84 persons previously reported<sup>5</sup> were utilized. Examination of the table reveals that in 11 of the extremities with varicose veins the rate of resting blood flow, in cubic centimeters per minute per hundred cubic centimeters of limb

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3. Holling, H. E.; Beecher, H. K., and Linton, R. R.: Study of the Tendency to Edema Formation Associated with Incompetence of the Valves of the Communicating Veins of the Leg: Oxygen Tension of the Blood Contained in Varicose Veins, *J. Clin. Investigation* **17**:555 (Sept.) 1938.

4. Abramson, D. I.; Zazeela, H., and Marrus, J.: Plethysmographic Studies on Peripheral Blood Flow in Man: I. Criteria for Obtaining Accurate Plethysmographic Data, *Am. Heart J.* **17**:194 (Feb.) 1939. Ferris, E. B., Jr., and Abramson, D. I.: Description of a New Plethysmograph, *ibid.* **19**:233 (Feb.) 1940.

5. Abramson, D. I., and Fierst, S. M.: Resting Blood Flow and Peripheral Vascular Responses in Hypertensive Subjects, *Am. Heart J.* **23**:84 (Jan.) 1942.



volume, fell within the range for the normal group (1.4 [mean] with a standard deviation of 0.5), while in 5 the rate was somewhat increased beyond this range. In those patients in whom the degree of involvement was different in the two legs, no relation could be observed between the severity of the process and the rate of blood flow. Further, in subject D.S., in whom there was unilateral involvement, the values were the same for the normal limb and for the one with varicose veins. In the few instances in which readings for the forearm were obtained, the rate of blood flow fell within the range for the normal group,  $1.8 \pm 0.7$  cc. per minute per hundred cubic centimeters of limb volume.

*Resting Blood Flow in Legs with Varicosities*

Subject	Age	Blood Flow, Cc. per Min. per 100 Cc. of Limb Volume		Degree of Involvement
		Normal Forearm	Involved Leg	
P. I. ....	41	...	1.2	4+
R. K. ..	51	...	1.5	4+
M. L. ....	41	1.4	2.3	2+
C. S. ....	35	...	1.1	4+
L. L. ....	..	...	1.7	2+
M. N. ....	49	...	1.3	2+
J. Z. ....	29	...	1.6 (right) 2.4 (left)	4+ 1+
S. C. ....	74	...	1.4	2 to 3+
D. S. ....	..	...	1.7 (left) 1.6 (right)	3+ Normal
S. L. ....	46	1.9	2.4	...
J. W. ....	63	...	1.8 (right) 1.3 (left)	3+ 2+
M. C. ....	67	...	2.0 (right) 1.1 (left)	3+ 1+
R. M. ....	60	1.5	2.4	3 to 4+

It is of interest that the 1 subject (not included in the table) who had markedly sclerotic veins of the upper extremity also had a normal rate of blood flow in the forearm (1.6 cc. per minute per hundred cubic centimeters of limb volume).

COMMENT

It is evident from these data that in our series of patients the circulation was not diminished in extremities with uncomplicated varicose veins. The findings, therefore, are not completely in accord with the view of de Takáts and his associates<sup>1</sup> that there is some interference with arterial blood flow in this condition, nor do they entirely support the opposite contention of Blalock,<sup>2</sup> who interpreted his data to indicate that an increased circulation is present.

As pointed out by a number of investigators,<sup>6</sup> the oxygen content of the blood in the large veins of the leg may not give a true representation of the oxygen content of the capillaries. It is possible that a shunting of blood directly from arterioles to venules may take place via the arteriovenous anastomoses, thus raising the total oxygen content of venous blood but at the same time actually diminishing the quantity available for tissue metabolism. This criticism, therefore, has been made in respect to determinations of blood flow based on the gaseous content of venous blood. However, it does not hold with regard to the venous occlusion plethysmographic method when applied to the leg, since an arterial occlusion pressure is maintained at the ankle during the period in which the circulation in the leg is being measured.<sup>7</sup> Inasmuch as the arteriovenous anastomoses in the lower extremity are for the most part limited to the foot, this procedure, which temporarily removes the distal portion of the extremity from the circulation, at the same time eliminates the variable factor of blood flow through these structures.

In view of our findings it does not seem reasonable to assume that the various cutaneous complications frequently present in an extremity with varicose veins result from a diminution of arterial circulation. The presence of venous and capillary stasis and the subsequent interference with the interchange of oxygen and waste products between the blood and the tissues<sup>1</sup> are probably a more likely explanation. Obviously, such a state would be conducive to an impaired nutrition of the tissues and hence a reduced resistance to infection. Further, the associated lymphatic obstruction also must be considered as playing an important role in the causation of the lesions.<sup>8</sup>

It must be reemphasized at this point that in most of the patients used in the present study cutaneous lesions were minimal or absent. Hence, the objection may be raised that data obtained on such subjects cannot be applied to the elucidation of the problem of these cutaneous complications. However, we still feel justified in stating that the varicosities by themselves do not contribute to the formation of ulcers insofar as any effect that they may have on the rate of arterial blood flow is concerned.

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6. Harpuder, K.; Stein, I. D., and Byer, J.: The Role of the Arteriovenous Anastomosis in Peripheral Vascular Disease, *Am. Heart J.* **20**:539 (Nov.) 1940. Holling, Beecher and Linton.<sup>9</sup>

7. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb: Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, *Clin. Sc.* **3**:119 (April) 1938.

8. Trout, H. H.: Ulcers Due to Varicose Veins and Lymphatic Blockage; New Principle in Treatment, *Arch. Surg.* **18**:2281 (June) 1929.

## SUMMARY AND CONCLUSIONS

The peripheral circulation has been investigated in a series of 14 patients with varicose extremities by means of the venous occlusion plethysmographic method.

The rate of blood flow in the involved limb was found to fall within the range of that for normal subjects or somewhat beyond it. In no instance was decreased peripheral circulation observed in the extremity with varicose veins.

It is suggested that the various cutaneous lesions associated with varicosities do not have their origin in a diminished arterial inflow.

Mrs. William Littleford gave valuable technical assistance.

Jewish Hospital.

# PROGRESS IN ORTHOPEDIC SURGERY FOR 1941

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE  
AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

(Continued from Page 862)

## XII. CONDITIONS INVOLVING THE LOWER PART OF THE BACK

*General Considerations.*—A review of the literature of 1941 relating to conditions involving the lower part of the back reveals a sustained interest in lesions of the intervertebral disks and their relation to sciatica and pain in the lower part of the back. The clinical diagnosis is stressed by a larger number of writers, and a trend toward less frequent use of contrast mediums is reflected. Atypical cases of herniated disks call for visualization. Operative procedures are less radical in extent. The relation of fusion operation and disk removals is debated at length, although a trend to a combined operation is sensed in many of the articles. Spondylolisthesis and lumbosacral anomalies drop far behind disk lesions as subjects discussed in the writings of the past year.

The question of contracted fasciae is either a closed book or is receding in importance if the number of essays on the subject is a true reflection of the interest of orthopedic surgeons. The same may be said regarding manipulative and injection therapy for conditions involving the lower part of the back. Fibrositis has been passed by, attracting the attention of but a small group of writers. These and even other pathologic entities are referred to chiefly in their relation to disks.

*Intervertebral Disks.*—Adson<sup>493</sup> gives a splendid review of the present knowledge of disks and a good anatomic consideration. He considers myelography with iodized poppyseed oil as most reliable but does not utilize this method extensively because of the dangers and the medico-legal significance. He advocates a trial of orthopedic management before resorting to operation. Hemilaminectomy is the usual approach. This is combined with spinal fusion if instability of the spine warrants it. Aird<sup>494</sup> advocates the use of a blood pressure cuff as a means of increasing the intracranial pressure to differentiate lesions of mechanical origin from others. A pressure of 40 mm. of mercury is maintained for ten minutes while the neurologic examination is repeated. Positive results were obtained in 41 of 45 cases with space-consuming lesions, and

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493. Adson, A. W.: Rupture of Intervertebral Disks as Cause of Low Back Pain and Chronic Recurring Sciatica, *Proc. Interst. Postgrad. M. A. North America* (1939), 1940, pp. 142-147.

494. Aird, R. B.: Prolonged Jugular Compression: Diagnostic Test of Neurologic Value, *Arch. Neurol. & Psychiat.* **45**:633-648 (April) 1941.

negative results were had in 54 cases in which such lesions were thought to be absent. [ED. NOTE: This is a useful test but is one to be applied with caution.] Barr and Mixter<sup>495</sup> try conservative treatment. In cases in which operation is required combined laminectomy and fusion give better results than laminectomy alone. Ninety-four cases in which the follow-up was for more than one year are reported. Of these there was freedom from sciatic pain in 77 per cent and only slight leg pain in 18 per cent. The relief of pain in the back was less satisfactory. Seventy-three per cent of the patients on whom combined operation was done had no pain in the back, while but 52 per cent of those on whom laminectomy was done were free of back symptoms. Cacchi<sup>496</sup> calls attention to a narrowing of the neural canal in hypertrophy of the ligamentum flavum as contrasted to the defect seen in the posterior protrusion of the disk. Healing is favored by the use of diathermy or infra-red rays and a diet rich in vitamins. [ED. NOTE: This is certainly only a possibility.] Craig and Walsh<sup>497</sup> state that the mobility of the nerve roots forming the cauda equina frequently allows abnormal pressure to cause pain without motor changes. Compression of a nerve root causes radicular pain, usually sharp, increased by coughing or sneezing and accompanied by local tenderness over the spine and by motor and sensory signs. Because of the sensory overlap section of a single root does not produce anesthesia. Lesions of nerve roots at the intervertebral foramens resulting from fracture, hypertrophic arthritis and spondylolisthesis must be kept in mind. Davis<sup>498</sup> finds the most common cause of pain radiating to the sciatic areas to be due to tumors of the cauda equina or arachnoiditis. De Morsier<sup>499</sup> states that urinary disturbances and sexual impotence are frequently associated with herniated disks. He found an inverse Lasègue sign in 2 cases. [ED. NOTE: Is an inverse Lasègue sign a negative one?] Esser<sup>500</sup> reports 3 cases of herniated disks.

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495. Barr, J. S., and Mixter, W. J.: Sciatic Pain in Low Back Derangements: Its Incidence, Significance and Treatment; Symposium; Posterior Protrusion of Lumbar Intervertebral Discs, *J. Bone & Joint Surg.* **23**:444-456 (April) 1941.

496. Cacchi, R.: Hernia of the Intervertebral Discs, Especially of Lumbar Segment: Surgical Therapy, *Gior. di clin. med.* **21**:1223-1249 (Dec. 30) 1940.

497. Craig, W. M., and Walsh, M. N.: Neuro-Anatomic and Physiologic Aspects and Significance of Sciatica, *J. Bone & Joint Surg.* **23**:417-434 (April) 1941.

498. Davis, L.: Neurosurgical Lesions: Diagnosis and Treatment of Those Producing Pain in Back, *Indust. Med.* **10**:55-58 (Feb.) 1941.

499. de Morsier, G.: Frequent Cause of Lumbago and Sciatica: Traumatic Dislocation of Lumbar Intervertebral Disks with Posterior Nuclear Hernia, *Rev. méd. de la Suisse Rom.* **60**:999-1011 (Nov. 25) 1940.

500. Esser, P. H.: Prolapse of Intervertebral Disks, *Geneesk. gids* **18**:748-753 (Aug. 30) 1940.

Heine<sup>501</sup> states that Luschka described prolapse of the intervertebral disk more than eighty years ago. Naffziger<sup>502</sup> finds minor bladder difficulties common in disk cases. Atrophy of the leg on the involved side is common. Jugular compression pain develops in 60 per cent of the cases. Air myelography is tried first, but if the result is debatable, 3 cc. of iodized poppyseed oil is used. Bradford<sup>503</sup> reports histologic studies of 20 herniations. Nucleus pulposus was found in all cases; the inner layers of the annulus fibrosus were found in 16 cases, and the outer layers, in none. He estimates that a total force of more than 1,600 pounds (725.75 Kg.) may be put on the lumbosacral disk when a man lifts a 100 pound weight (45.4 Kg.) with arms outstretched. Dandy<sup>504</sup> states that the great majority of injured intervertebral disks can be diagnosed and localized to the fourth or fifth lumbar interspaces by obtaining the history and making clinical examination alone and that exploration of these areas by a unilateral approach should be carried out without subjecting the patient to an accessory diagnostic test of myelography or even of simple lumbar puncture. The diagnosis is not always unequivocal, but the percentage of error should be small. During the eight months preceding the time of writing the author removed disks from 29 patients who had received no spinal injection.

In 10 cases Dandy found concealed disks with a protrusion too small to be shown by myelography. These disks are bound to the emerging spinal nerve by adhesions and are softer to touch than the normal disk. When the covering ligament is incised, forceps sink deeply into the intervertebral space with little pressure, and a mushy brownish material may be removed with a curet. Results of opening of the flat disks have not been so good as in large protrusions, probably because the incision allows gradual escape of the injured disk material. The existence of these concealed disks is another argument against myelography. Dandy has had no recurrences (of pain low in the back or sciatic pain?) and has never felt fusion to be advisable following the disk operation.

The use of myelography in the diagnosis of herniated disks is going through a transition. Various mediums are employed, notably air, oxygen, colloidal suspension of thorium dioxide, iodized poppyseed oil

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501. Heine, J.: Anterior Protrusion of Intervertebral Discs, *Chirurg* **12**:611-614 (Oct. 15) 1940.

502. Naffziger, H. C.: Diagnosis of Protrusions from Intervertebral Discs, *Proc. Interst. Postgrad. M. A. North America* (1940), 1941, pp. 122-125.

503. Bradford, F. K.: Certain Anatomic and Physiologic Aspects of Intervertebral Disc, *South. Surgeon* **10**:623-629 (Sept.) 1941.

504. Dandy, W. E.: Concealed Ruptured Intervertebral Discs: Plea for Elimination of Contrast Mediums in Diagnosis, *J. A. M. A.* **117**:821-823 (Sept. 6) 1941.

and other contrast substances. Some writers reserve myelography for the questionable cases, feeling confident that the clinical picture is diagnostic in 90 per cent of the cases. Other surgeons fear the pathologic and medicolegal complications which may arise from contrast mediums which cannot be completely removed. From the histologic point of view Benedek and Juba<sup>505</sup> describe an oleogranuloma found at autopsy following the injection of iodized poppyseed oil. Headley-Blythe and Anderson<sup>506</sup> warn of degenerative changes which follow the nonremoval of iodized poppyseed oil. In 2 cases secondary operations to relieve pain were necessary, and in 1 case necrosis of the cord was revealed at autopsy, possibly the result of contrast myelography. Kubik and Hampton<sup>507</sup> have removed the iodized poppyseed oil shortly after fluoroscopic examination in 30 cases by section. A delay in removal permits the oil to penetrate along the nerve sheaths. Lysterly<sup>508</sup> uses oxygen in the diagnosis of obscure lesions. Marcovich, Walker and Jessico<sup>509</sup> report on 150 patients who received from 2 to 4 cc. of iodized poppyseed oil. Forty-six and four tenths per cent had no immediate symptoms. Twenty-three patients had slight fever; pain was aggravated in 9; nausea occurred in 2; vomiting, in 2, and stiff neck, in 1. The spinal fluid cell count and total protein were elevated for at least several days following injection. The authors believe that opening of the dura contributes to rapid encystment of the oil. Nichols<sup>510</sup> does not feel that air myelography is reliable and has used 5 to 10 cc. of colloidal suspension of thorium dioxide. From 70 to 90 per cent is removed by immediate forced drainage. [ED. NOTE: Films obtained by this method are clear and reveal much more detail than those resulting from the use of the more contrasty iodized poppyseed oil.] Scott and Young<sup>511</sup> advocate air myelography with films taken during extension and flexion. They

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505. Benedek, L., and Juba, A.: "Late Block" During Myelography with Lipiodol (Iodized Oil), *Deutsche Ztschr. f. Nervenhe.* **151**:55-62, 1940.

506. Headley-Blythe, J., and Anderson, C.: *Lipiodomania*, M. Press **205**: 122-123 (Feb. 5) 1941.

507. Kubik, C. S., and Hampton, A. O.: Removal of Iodized Oil by Lumbar Puncture, *New England J. Med.* **224**:455-457 (March 13) 1941.

508. Lysterly, J. G.: Herniation of Intervertebral Disk, *J. Florida M. A.* **27**:491-500 (April) 1941.

509. Marcovich, A. W.; Walker, A. E., and Jessico, C. M.: Immediate and Late Effects of Intrathecal Injection of Iodized Oil, *J. A. M. A.* **116**:2247-2254 (May 17) 1941.

510. Nichols, B. H.: Symptoms and Diagnosis of Herniated Nucleus Pulposus, *Proc. Interst. Postgrad. M. A. North America* (1940), 1941, pp. 367-369.

511. Scott, M., and Young, B. R.: Sciatic and Low Back Pain: Diagnostic Value of Air Myelogram, *J. M. Soc. New Jersey* **38**:24-26 (Jan.) 1941.

explain remissions of sciatica as resulting from the mobile disks. [ED. NOTE: The long remissions must be due to other factors; otherwise the episodes would be of short duration and would recur several times daily in active persons.] Weber<sup>512</sup> injects 60 to 80 cc. of air into the epidural space via the sacral hiatus. The results were not satisfactory in a limited number of cases. Echols<sup>513</sup> discards total protein determinations and reserves myelography for atypical cases.

*Sciatica.*—Auersperg<sup>514</sup> classifies sciatica as intervertebral (radicular sciatica), intrapelvic (funicular sciatica), extrapelvic (peripheral sciatica) and symptomatic. In the last named, the reaction is direct from continuous destructive processes; in essential sciatica it is indirect from a distance. Bauer and Hellsten<sup>515</sup> infiltrate the lumbar sympathetic chain of the affected side for rapid relief of idiopathic sciatica. Blewett<sup>516</sup> demonstrates the narrowing of the lumbosacral disk space and anterior slipping of the fifth lumbar vertebra in the upright position in 2 cases of sciatica complicating spondylolisthesis [ED. NOTE: Comparison of roentgenograms taken with the patient in the supine and in the upright position is most valuable in diagnosing such lesions.] Brocker<sup>517</sup> is inclined toward the theory of the vertical origin of sciatica inasmuch as he rarely finds inflammatory lesions of the nerve at this level, whereas sacro-lumbar degenerative articular changes are common. Bumm<sup>518</sup> believes sciatica is frequently due to a synergy of various causes. Thus the initial lesion may be that of compression followed by infection. He feels that in 90 per cent of the cases sciatic pain is due to arthritis of the interapophysial articulations as emphasized by Putti. Scoliosis is often associated with sciatic pain and in many instances is the cause rather than the result of the sciatic symptoms. [ED. NOTE: The relation of synovitis of the lateral articulations at the lumbosacral level to sciatica is often overlooked. It is reasonable to assume that inflammatory synovial reactions adjacent to the roots of the lumbosacral plexus may be referred to the sciatic nerve.]

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512. Weber, H. M.: Epidural Air Injection in Diagnosis of Spinal Canal Masses, California & West. Med. **54**:27 (Jan.) 1941.

513. Echols, D. H.: Neurosurgical Treatment of Sciatic Pain with Notes on Fifty Consecutive Cases, New Orleans M. & S. J. **94**:265-270 (Dec.) 1941.

514. Auersperg, A.: Symptomatology Aspects of Sciatica, Wien. klin. Wchnschr. **53**:951-953 (Nov. 15) 1940.

515. Bauer, G., and Hellsten, W.: Procaine Hydrochloride Block of Lumbar Sympathetic as Adjuvant Therapy in Lumbago-Ischialgia: Preliminary Report, Nord. med. (Hygiea) **9**:601-603 (Feb. 22) 1941.

516. Blewett, J.: Cases of Spondylolisthesis of Unusual Interest, Brit. J. Radiol. **13**:416-421 (Dec.) 1940.

517. Brocker, J. E. W.: Sciatica of Vertebral and Nervous Origin, Helvet. med. acta **7**:355-420 (Oct.) 1940.

518. Bumm, E.: Etiology and Pathogenesis of Sciatica, Med. Welt **14**:814-817 (Aug. 10) 1940.



Grunbaum<sup>519</sup> injects into the sciatic nerve large quantities of physiologic solution of sodium chloride and has had favorable results. When the sciatica is predominantly fibular in location, the injection is made 6 to 8 cm. from the head of the fibula. Cures in 70 per cent of the cases are reported. Guk,<sup>520</sup> using the technic of Vichneoski, has employed procaine hydrochloride block in 84 cases of sciatica. In 64 cases two blocks six days apart were sufficient; in the other cases one block sufficed. In 50 of Kellgren's<sup>521</sup> 70 cases ligamentous or muscular lesions were found; in 15 there were displaced intervertebral disks, and in 5 there were miscellaneous diseases. In no case could the pain be ascribed to interstitial neuritis of the sciatic disease. The author believes this entity rare or nonexistent. Livingston<sup>522</sup> locates a trigger point in the multifidus triangle in the lower sacral area. He has given 14 patients repeated injections with 5 to 10 cc. of 2 per cent solution of procaine hydrochloride. The results were good. Thurel<sup>523</sup> finds that in epidural injections of procaine hydrochloride for therapeutic purposes, the pain is always reawakened when the fluid comes in contact with the painful nerve. Ferrandu and Forni<sup>524</sup> experimenting with sterile bile injections into the sciatic nerve of rabbits found peripheral degenerative processes.

Odom and Kolczum<sup>525</sup> describe a type of nerve block which they have found to be effective, namely, epidural injection of procaine base in almond oil in cases of sciatica in which no mechanical lesion is demonstrable. With the patient sitting erect and the area anesthetized with 1 per cent procaine hydrochloride solution, a needle is introduced into the second lumbar interspace. Entrance into the spinal canal is determined by negative pressure as shown by a liquid in a glass tube attached to the needle. Twenty cubic centimeters of 2 per cent procaine base in almond oil is then injected. This treatment was used in 42 cases in which the duration of the sciatic pain ranged from

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519. Grunbaum, R.: Treatment of Sciatica with Special Reference to Injection of Large Amount of Physiologic Salt Solution, *Rev. neurol. de Buenos Aires* **5**:147-150 (April-June) 1940.

520. Guk, V. T.: Procaine Hydrochloride Block in Therapy of Lumbago and Sciatica, *Gaz. clin.* **38**:331-332 (Sept.) 1940.

521. Kellgren, J. H.: Sciatica, *Lancet* **1**:561-564 (May 3) 1941.

522. Livingston, W. K.: Back Disabilities Due to Strain of Multifidus Muscle: Cases Treated by Injection of Novocain, *West. J. Surg.* **49**:259-265 (May) 1941.

523. Thurel, R.: A Constant Pathognomonic Sign of Sciatica with Renewal of Pain upon Epidural Injection, *Rev. neurol.* **72**:466, 1940.

524. Ferrandu, S., and Forni, G.: Peripheral Degenerative Neuritis Due to Application of Sterile Bile on Trunk of Sciatic Nerve of Rabbit, *Ann. ital. di chir.* **19**:675-679 (July-Aug.) 1940.

525. Odom, C. B., and Kolczum, M. C.: Treatment of Idiopathic Sciatica by Epidural Injection of Almond Oil and Procaine, *South. M. J.* **34**:1149-1151 (Nov.) 1941.

one month to seven years. Forty-one of these patients, or 97 per cent, secured immediate relief from the injection. Lasting relief over a period of twenty to thirty-six months was obtained in 38 cases, or over 90 per cent. The authors also gave injections of iodized poppyseed oil in 10 cases to show the diffusion of solution into the epidural space and found that in all cases the diffusion was more rapid on the affected side than on the unaffected side. The reason for this is not clear. The authors recommend that this treatment be employed for relief of pain before other more radical procedures are attempted.

Ober<sup>526</sup> and Pickett<sup>527</sup> stress the importance of physical therapy in cases of conditions involving the lower part of the back and employ some form of fasciotomy in cases in which the condition is resistant.

Pribek<sup>528</sup> upholds the value of skin temperature determinations in differentiating sciatica from lumbago. Badgley<sup>529</sup> has made an exhaustive study of a long series of cases of sciatica and concludes:

The radiation of the pain in so-called sciatica is not nerve root irritation but is plexus in distribution. . . . There is a possibility that the radiation may be due to a referred mechanism from stimulation of peripheral pain fibers in the muscles, ligaments or articulations of the low back with central localization through overflow into the fibers from the postaxial surface of the leg.

*The Lumbosacral Joint.*—Spondylolisthesis has received little attention in the literature of 1941 and does not compete effectively with the disk wave which engulfs us for the present. Burckhardt<sup>530</sup> uses the term "spondylolisthesis imminens" to designate cases of spondylolysis. He believes the defect of the isthmus is of congenital origin and that symptoms may appear spontaneously or be released by trauma. He reports 63 cases. Nagura<sup>531</sup> attributes the spondylolisthesis to an original interruption of the continuity of bone at the isthmus with replacement by fracture-healing processes in the cartilage. Breck<sup>532</sup> emphasizes the greater incidence of lumbosacral lesions as compared with lesions of the

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526. Ober, F. R.: Salvaging Lame Back Patient, Arch. Phys. Therapy **22**:583-586 (Oct.) 1941.

527. Pickett, J. C.: Role of Fascia in Low Back Pain, South. Surgeon **10**: 738-746 (Oct.) 1941.

528. Pribek, L.: Cerebrospinal Fluid Findings and Skin Temperature Measurements in Differential Diagnosis of Sciatica, Klin. Wchnschr. **20**:320-321 (March 29) 1941.

529. Badgley, C. E.: Some Significant Anatomical Facts of Importance in Study of Sciatica, Univ. Hosp. Bull. Ann Arbor **7**:95 (Nov.) 1941.

530. Burckhardt, E.: Spondylolisthesis, Schweiz. med. Wchnschr. **70**:1093-1101 (Nov. 16) 1940.

531. Nagura, S.: Spondylolisthesis in Light of Cartilaginous Callus Formation, Beitr. z. klin. Chir. **171**:346-353, 1940.

532. Breck, L. W.: Newer Aspects of Low Back Pain, Southwestern Med. **24**:401-404 (Dec.) 1940.

sacroiliac joint as the source of pain in the lower part of the back. The downward subluxation of the fifth lumbar vertebra on the sacrum associated with narrowing of the lumbosacral disk is important. The author outlines treatment as described by Williams to flex the lumbar spine reducing the lordosis. Harris<sup>533</sup> holds that the mechanical weakness, increased lumbosacral angle and narrowed disk as well as the posterior rotation of the pelvis are the chief factors causing pain in the lower part of the back. Wichtl<sup>534</sup> states that all intervertebral disks are subject to physiologic aging. This is especially true at the lumbosacral juncture (osteochondrosis). The clinical significance of this condition lies in the presence of sciatic symptoms probably related to the intervertebral articulations. The narrowed lumbosacral disk is attributed to physiologic growth and involution processes as has been observed in the disks of the sacrum. Sacralization of the last lumbar vertebra was studied by Gabetti.<sup>535</sup> In 855 pelves, 78 cases of sacralization were found, 49 bilateral and 29 unilateral.

Patients with painful symptoms received daily epidural injections of 10 cc. of a solution of 0.25 per cent cocaine, 0.5 per cent phenol and 0.75 per cent sodium chloride solution. Five patients were subjected to resection of the transverse processes with good results.

Discussions of the sacroiliac joint are conspicuous by their absence, but there are one or two articles of general scope. These reveal nothing new.

*Causalgic Backache.*—Hudson, Hettesheimer and Robin<sup>536</sup> describe causalgic backache. Unilateral pain in the upper lumbar region, aggravated by recumbency awakening the patient at night and accompanied by pain radiating along the twelfth rib and to the groin, is a definite symptom complex. The findings are downward tilt of the pelvis on the painful side, increased lordosis, postural scoliosis, abduction and internal rotation of the thigh on the affected side. Tenderness and hyperesthesia are present along the twelfth dorsal and first lumbar nerves. The mechanism is described as due to a spasm of the quadratus lumborum muscle resulting in compression or tension of the twelfth dorsal and first lumbar nerves. Thirty patients treated by elevating the heel on the low side are reported to have been relieved.

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533. Harris, H. W.: Low Back Pain, *J. Med.* **21**:469-471 (Jan.) 1941.

534. Wichtl, O.: Reduction in Width of Last Lumbar Disk and Occurrence of Lumbosacral Transitional Disks: Relation to Sacralization, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **62**:229-247 (Oct.) 1940.

535. Gabetti, D. C.: Therapy of Painful Sacralization of Fifth Lumbar Vertebra, *Arch. per le sc. med.* **71**:105-156 (Feb.) 1941.

536. Hudson, O. C.; Hettesheimer, C. A., and Robin, P. A.: Causalgic Backache, *Am. J. Surg.* **52**:297-303 (May) 1941.

*Ligamentum Flavum.*—Mensor and Fender<sup>537</sup> discuss the ligamentum flavum from the anatomic point of view and its relation to pain in the lower part of the back. They present the results of studying ligamenta flava which were removed from 26 patients at operation, measured and examined microscopically. These specimens were taken regardless of whether they were suspected of causing backache. Specimens from cadavers in various age groups without known history of back trauma were also studied. The authors think that the size and the thickness of the ligamentum flavum alone are unimportant as possible causative factors in back pain and sciatica unless changed by trauma or disease or causing pressure symptoms in combination with skeletal or disk changes or both. They feel that measurements of the ligamentum flavum are of little value because of technical factors which prevent the establishment of any fixed standard and because the size and thickness have been shown to vary with age, anatomic and pathologic structural changes and location in the individual case. From their microscopic studies the authors conclude that the ligamentum flavum reacts to disease or trauma by a loss of the normal structure of its elastic fibers and the development of a substitution fibrosis with replacement by collagen elements. Definite degenerative factors occur in the ligamentum flavum with advancing age, giving pathologic changes similar to those seen in trauma and disease. The authors feel that hypertrophy is an unsuitable term as no increase in elastic elements with preservation of a normal histologic appearance has been observed. The authors have demonstrated a definite nerve supply chiefly nonmedullated in type to the ligamentum flavum.

XIII. CONDITIONS INVOLVING THE SPINE AND THORAX,  
EXCLUSIVE OF THOSE IN THE LOWER  
PART OF THE BACK

*Causes of Scoliosis.*—The causation of so-called idiopathic scoliosis still remains unknown, and the failure of general agreement among those working with cases of this condition is well shown by Shands, Barr, Colonna and Noall<sup>538</sup> in their study of the end results of treatment. In a survey of sixteen orthopedic clinics throughout the country an expression of ideas concerning the causation of the idiopathic type of scoliosis has been obtained from the workers in the clinics, and these views have been divided into five general groups as shown in the table hereinafter reproduced.

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537. Menson, M. C., and Fender, F. A.: *Ligamentum Flavum: Its Relationship to Low Back Pain*, Surg., Gynec. & Obst. **73**:822-827 (Dec.) 1941.

538. End Result Study of Idiopathic Scoliosis: Report of Research Committee, J. Bone & Joint Surg. **23**:963-977 (Oct.) 1941.

[ED. NOTE: It is interesting, however, to see that the majority of clinicians feel that there is at least some associated metabolic disturbance as a factor and that fewer workers believe that unrecognized poliomyelitis is the major cause of idiopathic scoliosis. It is worthy of note that apparently six of the clinicians still hold to the old belief that "prolonged sitting in school" is an important factor. Most investigators who have been studying the problem of scoliosis during the past few years do not feel that the idiopathic type is appreciably influenced by postural faults, especially those associated with prolonged sitting in school. It is more generally felt that it is a condition of unrecognized causation

*Etiology*

Probable Etiology of Idiopathic Scoliosis	Clinicians Supporting View
Curvature is the result of failure of muscular and skeletal systems to maintain a balance during the rapid growth period, and is associated in some way with an endocrine or metabolic disturbance.....	4
Curvature is primarily the result of muscle imbalance, the source of the imbalance being unexplained, but possibly being postural fatigue, and unrecognized poliomyelitis, or some similar process.....	7
Curvature is the result of a growth disturbance at the epiphyseal plate of the vertebrae, possibly related to an osteochondritic process or to epiphyseal trauma with an associated deficiency, either metabolic or dietary.....	6
Curvature is the result of postural faults, acquired during growth and fatigue of adolescence, prolonged sitting in school, etc., which gradually lead to a fixed deformity .....	6
Curvature is an exaggeration of physiologic deviation occurring during normal gait, being greater toward the right side due to the weight of organs, and passing beyond normal limits in the presence of some body insufficiency....	2
Hereditary and environmental factors are felt to be definitely contributory....	2

occurring during adolescence and usually self limited as to progress, although the end result of the deformity may be slight or severe.]

Farkas <sup>539</sup> reports a study of physiologic scoliosis. He points out that Sabatier found that the great majority of adult spines show a well defined curve to the side and that in the lumbar and cervicothoracic segments the convexity is usually to the left side and in the thoracic region to the right side. Farkas has studied 20 complete normal skeletons, ranging from 19 to 86 years of age. He has confined his studies to the vertebrae alone and concludes that the postnatal regular asymmetric development of the human spine is due to some powerful automatic function which becomes established just prior to the age of 6 years. He states that physiologic scoliosis is a postnatal development,

<sup>539</sup>. Farkas, A.: Physiological Scoliosis, J. Bone & Joint Surg. **23**:607-627 (July) 1941.

that it is not due to the regular variation of the normal or to the innate formative energy of the cells or to the proximity of another organ, such as the descending aorta, but that it is caused by a function continuously at work. Farkas also states that in 100 spines reviewed none were without a more or less marked lateral curve, although no 2 spines were found with identical lateral curves. He believes that the human gait is the cause of physiologic scoliosis. [ED. NOTE: This is an interesting study and brings up many questions about the possible causation of so-called idiopathic scoliosis. However, this physiologic scoliosis must not be confused with pathologic scoliosis, and it remains to be shown whether these conclusions regarding physiologic scoliosis have any significant bearing on the production of idiopathic scoliosis.]

Wenger and Herman<sup>540</sup> have studied the roentgen films of 256 cases of scoliosis following thoracoplasty operations at Sea View Hospital, Staten Island, N. Y. They believe that it is not necessary to resect the transverse processes for adequate cavity closure and suggest that the operation be modified to leave the transverse processes unharmed. They conclude that the removal of the transverse processes is the main cause of scoliosis following thoracoplasty. They also suggest that to insure against spinal deviation in cases in which the dorsal intrinsic musculature is unsatisfactorily or inadequately developed the periosteum of the ribs should be immobilized to the tips of the transverse process below its own level so that when regeneration of bone does occur it will act as an internal splint.

[ED. NOTE: It has been previously suggested that the scoliosis following thoracoplasty is the result of the disturbance of the muscle and bone balance. While it is obviously true that the muscular attachments to the transverse processes are a definite factor, the ribs and their muscular attachments have undoubtedly an important mechanical bearing on the production of scoliosis in these cases. It seems that further study is necessary to establish the importance of the transverse processes as the major factor in post-thoracoplasty scoliosis. In 1 of the cases presented six ribs were resected on one side and seven on the other at the same level, but scoliosis did not develop. The authors conclude that this was because the transverse processes were not disturbed. However, one would expect no curve to develop in such a case; if an equal disturbance of bone-muscle balance resulted on each side, it would not matter whether ribs or transverse processes were removed. It should be noted also that in many of these cases it is difficult to determine accurately from roentgen study actually how much, if any, of the transverse processes has been destroyed. The authors may be correct in

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540. Wenger, H. L., and Herman, M.: Role of Transverse Process in Thoracogenic Scoliosis, *Quart. Bull., Sea View Hosp.* 7:45-55 (Oct.) 1941.

stating that it is not necessary to remove the transverse process in order to get adequate collapse of the chest after thoracoplasty. The removal of the transverse process may be a factor in making the curve greater, since there is greater destruction of muscle attachment and bony leverage. However, it seems likely that the major problem in the production of post-thoracoplasty scoliosis is the disturbance of the bone-muscle balance due to the removal of the ribs and their muscular attachments rather than to the removal of the transverse processes alone.]

*Paralytic Scoliosis.*—Colonna and vom Saal<sup>541</sup> report a study of 500 cases of poliomyelitis and review the findings in a series of 150 patients with paralytic scoliosis. They analyze some of the mechanical factors involved in the development and the treatment of the lesions. They attempt to determine the reason for the development of the curvature and its possible prevention and treatment. They report that 62 per cent of all their cases of scoliosis were due to poliomyelitis. [ED. NOTE: This is a much higher incidence of poliomyelitis scoliosis than that of other clinics and may have been due to the facts that the cases of poliomyelitis were more severe and that the patients came for treatment of the scoliosis or other deformities while many patients with idiopathic scoliosis, which is often milder, might not have been sent to the clinic for study. In some clinics the incidence of poliomyelitis scoliosis is about 5 per cent, while the number of patients admitted for operation may represent 50 per cent because of the greater need for treatment and other factors.] The authors are impressed by the effect of the hip and shoulder muscles on the production of paralytic scoliosis and show illustrations of curvatures apparently due to contracture of muscles on the concave side and other curves due to contractures on the convex side. They report 28 cases of paralysis of the trapezius muscle and 42 cases of paralysis of the rhomboid muscles. Paralysis of the deltoid muscle gave rise to a curve toward the sound side in 23 of 45 cases. They also state that in addition to the pull of the asymmetric muscle forces, the uncomplicated inequality of the length of the legs is sometimes sufficient to initiate the process. Unequal length of the legs is felt to have been the primary factor in 22 cases in this series.

[ED. NOTE: It is difficult to agree with some of these conclusions. Since the shoulder girdle is hung from the trunk when at rest in the upright position, one would not expect to see structural scoliosis develop as a result of the paralysis of the shoulder muscles alone. Patients with paralysis of the deltoid and other shoulder muscles (e. g. those with

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541. Colonna, P. C., and vom Saal, F.: Study of Paralytic Scoliosis Based on Five Hundred Cases of Poliomyelitis, *J. Bone & Joint Surg.* **23**:335-353 (April) 1941.

Erb's paralysis) usually have little if any scoliosis, and if they do have it, it is of the functional type. Also, patients with amputation of the shoulder and resulting muscle imbalance are usually able to hold the spine straight although postural scoliosis during activity may develop. It should also be pointed out that there are many trunk muscles the asymmetric involvement of which may be impossible to estimate. It is difficult or impossible in any case of paralytic scoliosis to tell absolutely what muscles are involved in the first place, and as has been pointed out by others previously, the permutations and the combinations of possible muscle paralysis make the accurate estimate of the resulting force impossible. It should also be pointed out that an uncomplicated short leg causes functional scoliosis, convex to the side of the short leg when the patient is standing, and that this scoliosis disappears when the patient sits erect if the pelvis is level. It is hard, therefore, to accept the statement that "unequal leg length was felt to be the primary factor in 22 cases in this series." The short leg may have added to the problem of scoliosis due to paralysis of some of the intrinsic muscles of the trunk which it may have been impossible to detect as asymmetrically involved. But if the short leg were an important factor in producing structural scoliosis in persons with poliomyelitis, then one would expect all persons with poliomyelitis with short legs to have structural scoliosis. Functional scoliosis due to short leg represents an entirely different problem from the structural scoliosis following asymmetric paralysis of the muscles supporting the spine.]

Bisgard<sup>542</sup> again calls attention to the problem of chest and spine deformities, especially scoliosis, resulting from thoracic disease and operation. He divides thoracogenic scoliosis into two types: pleurogenic and thoracoplastogenic, the pleurogenic being due to

. . . pleural scar resulting from chronic pleuritis from any cause, such as a simple serous tuberculous effusion or tuberculous or nontuberculous empyema . . . [which] contracts gradually and through adherence to the ribs pulls them centripetally.

[ED. NOTE: Although the author does not mention it, he probably includes the cases due to actual fusion of the ribs on the concave side of the curve following osteomyelitis of the ribs after rib resection and drainage under the same heading as those cases due to scar contracture caused by pleuritis. It should be mentioned that scoliosis following empyema may be of two separate types, the one due to a greatly thickened and contracted pleura (often actually calcified) and the other due to fusion of two or more ribs on the concave side of the curve.]

Bisgard states that both pleurogenic and thoracoplastogenic scoliosis are preventable and are curable if corrected in their incipient stages

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542. Bisgard, J. D.: Deformities of Chest and Spine Resulting from Thoracic Disease and Operation: Their Prevention, *Am. J. Surg.* 54:317-325 (Oct.) 1941.



but extensive and rigid deformities of the spine and the costal framework are incurable. He states:

Pleurogenic deformities can be prevented by (1) the prevention of the formation of pleural scar by early cure of the empyema or pleuritis, and (2) the constant attention to maintenance of straight alignment or preferably of over correction of the spine. This can be accomplished by means of (a) postural wedging, (b) corrective body casts of plaster of Paris, and (c) resection of ribs on the side of concavity. To facilitate correction and the use of corrective measures, it is helpful to anesthetize the area of the wound by crushing the intercostal nerves which supply that area.

[ED. NOTE: It seems important to stress the postoperative care following thoracoplasty or empyema operations, as pointed out by Bisgard. The patients are usually treated by the thoracic surgeon and are not seen by the orthopedic surgeon until after a real problem of scoliosis has developed. Since most of the severe curvatures following these operations develop in children and because of the growth factor to be considered, it probably is important in some cases to continue the use of corrective plaster jackets and other measures as suggested by Bisgard for even longer periods, e. g. six to nine months postoperatively. It should be pointed out also that in some cases in spite of the best conservative care severe scoliosis may develop following rib resection for empyema or thoracoplasty, especially in children. It is necessary to resect fused ribs to correct some of these severe curvatures, and following correction of either type in the cases in which the condition is in a late stage spinal fusion is necessary to maintain any correction obtained in the curve. In some cases, especially those in which the patients are children, if severe curvature is expected to develop, it may be worth considering fusion of the spine before thoracoplasty.]

Schaefer and Purcell<sup>543</sup> state that it is possible to prevent entirely many of the cases of so-called idiopathic scoliosis or to preclude the aggravation of an existent curvature to be ameliorated if early diagnosis is made and treatment with desiccated thyroid instituted at its recognition. They point out that corrective orthopedic measures must be employed when gross deformity is demonstrated either by physical or by roentgen examination. The authors feel that treatment with desiccated thyroid is important in arresting the progress of so-called idiopathic scoliosis and quote Dr. H. L. Ulbrich's roentgen report to the effect that the epiphysial changes in the spine are the cause of progressive scoliosis and are of endocrine origin. [ED. NOTE: There is not sufficient evidence in this paper to warrant these conclusions.]

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543. Schaefer, R. L., and Purcell, F. H.: Juvenile Osteochondral (Chondro-Epiphysitis) Hypothyroidism, *Am. J. Surg.* **54**:589-604 (Dec.) 1941.

*Treatment of Scoliosis.*—LeMesurier<sup>544</sup> reports a method for correcting the deformity in scoliosis before performing the fusion operation. The author states that the only thing really new in his paper is the use of the hammock for correcting the curve and holding of the patient while the plaster jacket is being applied. This method has been used in 27 cases and has been found to be considerably more satisfactory than the turnbuckle jacket. The author points out that the most satisfactory method available for treating scoliosis, particularly in those cases in which the deformity is already fairly marked and almost certain to become worse is the method that has been developed over a period of years at the New York Orthopaedic Dispensary and Hospital. There are three main principles that govern this method of treatment: first, to find out which is the primary curve; second, to make this primary curve as straight as possible, and finally, to stiffen this curve permanently in the straightened position by a fusion operation. The author states that the most difficult part of the whole treatment is the straightening of the primary curve. In most cases in which this method is used, the primary curve has become so stiff that it cannot be straightened completely. It can be improved a good deal, particularly toward its ends, by bending the spine in the opposite direction, but there is a limit to the amount of improvement that can be obtained. So far as the author has been able to find out by using different amounts of bending force and observing the results on roentgenograms, increasing this force straightens the curve until a certain point is reached; then the correction stops rather suddenly. Any greater force will not produce any further correction of the primary curve, although it may increase the more flexible secondary curves. [Ed. NOTE: A greater force which did increase the more flexible secondary curve might be desirable in many cases in order to include some of the necessary compensation within the fusion area and therefore decrease the amount of compensation necessary below and above the fusion area.] The author states also that the Risser jacket can by a turnbuckle be made to exert a great deal of force but that this great force is not necessary and is sometimes dangerous. Besides involving difficulty of pressure sores, he feels that the whole method with the Risser jacket seems unreasonably complicated, requires a great deal of attention and takes a fairly long time before the patient is ready for the fusion operation. In an attempt to overcome these objections, the author reports the use of a hammock for the correction of these curvatures. The patient is placed in the hammock for an increasing length of time each day until he becomes

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544. LeMesurier, A. B.: A Method of Correcting the Deformity in Scoliosis Before Performing the Fusion Operation, *J. Bone & Joint Surg.* **23**:521-532 (July) 1941.

used to the position, the two ends of the hammock being swung up to the ceiling with the body bent rather sharply in the direction to correct the primary curve. He points out also that this method is no more efficient in correcting the primary curve than is the Risser jacket, but the author believes that it is just as efficient and that it has certain advantages. He states that several attempts have been made to obtain more correction of the stiff curves than can be obtained by the hammock alone, but without success. [ED. NOTE: It should be pointed out that patients put up in this type of hammock have the head and the neck as well as the pelvis markedly flexed toward the side of the convexity of the primary curve. If turnbuckles are then placed in this position, it causes a great stretch on the neck, and it probably is impossible to obtain further correction without too much stretch on the cervical area.]

The author is, therefore, convinced that the stiff primary curves can be corrected to a certain limit by a moderate amount of bending force, and cannot be corrected further by any reasonable force that the patient can stand. The amount of bending force required to correct the curve to its limit can be as well obtained in the hammock, as it can with the turnbuckle jacket, or with any other mechanical force applied externally.

[ED. NOTE: This is an interesting paper, and the author presents a complete report of his method and shows roentgenograms of excellent correction by this technic. It is noted, however, that his illustrations show the patient markedly flexed toward the side of the convexity of the primary curve, with marked flexion of the cervical vertebra and especially of the head toward the side of the convexity. This suggests the possibility of cervical and brachial plexus problems or possibly subluxation of the cervical vertebrae as complications with this method. These may be fairly well controlled with the turnbuckle jacket method, especially when the turnbuckle jacket is applied with the patient's head and trunk flexed to the side of the concavity. When the turnbuckle jacket is used in this way, there will not be such sharp flexion of the head and the neck toward the side of the convexity with stretching of the cervical and brachial plexus during correction. The author's method has an advantage in that the patient can be flexed and corrected and the operation done without the period of correction in plaster requiring hospitalization for some weeks, as is usually necessary when the turnbuckle jacket is used. The method has, however, the disadvantage of including the whole leg and knee on the side of the convexity, therefore, immobilizing the knee and the ankle for several months. This method has been entirely satisfactory in the author's opinion, and it will be interesting to see whether it takes the place of the more commonly used turnbuckle jacket. In most hospitals in which the turnbuckle

jacket is used extensively and in large series of cases, the problem of pressure sores and other complications has been largely eliminated, so that as a rule this has not been a serious problem. It is true that in some cases correction can be easily achieved, especially those in which there are mild curves, and the hammock method of treatment described in this article may be satisfactory in cases of that type. However, it is likely that the turnbuckle jacket will continue to be used, especially in cases in which the condition is severe in which an attempt to obtain the maximum amount of correction should be made. Although a comparison of the two methods has not been made in a large series of cases presenting difficult problems, it seems most likely that the turnbuckle jacket method would obtain better results in cases in which the condition is severe when one considers the mechanical forces being used.]

Shands and associates<sup>538</sup> report an end result study of treatment of idiopathic scoliosis. This study included 425 case histories with roentgenograms and photographs. End result physical examination was made of 127 of the patients. The cases were reviewed from the standpoint of end results in sixteen orthopedic clinics throughout the country so that the report gives a good cross section of the methods of treatment, end results and various other statistics summarizing many of the present concepts regarding the treatment of idiopathic scoliosis. This is an excellent report and should help to clarify many of the problems of scoliosis. Some of these statistics confirm the previously noted observations, such as the facts that cosmetic deformity is the chief complaint, that the patients generally have no other symptoms, that it is a disease appearing most frequently at the age of puberty and predominating in girls 4 to 1 and that the curve is to the right in about 80 per cent of the cases, most commonly in midthoracic region. In this series all types of treatment were used, symmetric and asymmetric exercises, supports, correction and fusion and combinations of all types. Fifty per cent (214) of the patients reviewed had fusions done either immediately or after conservative treatment had been abandoned in favor of operation. Correction was by means of turnbuckle jacket in 80 per cent of those corrected and fused. The average percentage of those fused was 65, and the average percentage at end result examination was 27.

It is interesting to note that the patients showed considerable variation in the period of recumbency and that there was much less loss of correction in those kept recumbent three to six months and over post-operatively. Recumbency for six months or more did not seem to reduce materially loss of correction in this series.

. . . It was generally felt that immobilization during recumbency in plaster jackets is the best method of maintaining correction. Support should be continued after the patient becomes ambulatory for a total period of 7 to 9 months to

allow fusion mass to become solid since it must resist not only the strain of superincumbent weight but the tendency of contractures to pull the spine back to the deformed position. Ordinary back braces apparently do not maintain correction during this period unless they incorporate some lateral force as well as support. The results also show that those in whom fusion was less than the primary curve lost more than those in whom all the primary curve was fused. The greatest amount of correction was maintained in those patients in whom the area of fusion included more than the primary curve.

In patients in whom the extent of fusion was less than the primary curve 75 per cent lost 0 to 35 degrees. When the fusion was the same as the primary curve, 94 per cent lost 0 to 35 degrees, and when fusion was greater than the primary curve, 95 per cent lost 0 to 35 degrees.

[ED. NOTE: It is generally accepted that the primary curve is the minimum fusion area, and when less than this area is fused, the curve may definitely increase or lose correction for this reason. Loss of correction when the whole or more than the primary curve is fused must be due to inadequate fusion operation technic, failure to maintain the corrected position for a sufficient time or actual failure of fusion with pseudarthrosis.]

This report also reveals a high percentage of pseudarthrosis, a total of 60 cases, or 28 per cent, among 214 cases in which fusion was done for scoliosis. [ED. NOTE: This is a high percentage of pseudarthrosis following fusion for scoliosis. It is interesting to note that the percentage was lowest following the McKenzie-Forbes procedure—23 per cent. It should be noted that these figures cover the operations done by many surgeons over a long period of years during which the method of fusion has changed considerably. The results following fusions during the past few years show a much smaller incidence of pseudarthrosis, at least in some clinics.]

This study reports that complete correction was gained in only 5.5 per cent of the cases in which correction was done; all of the correction was maintained in 8 per cent, and there was complete loss of correction in 29 per cent. [ED. NOTE: It is of course obvious that only the relatively milder curves can be completely corrected and that the tendency to loss of correction should be less in these milder curves following correction than in the more severe curves.]

Results in 69 per cent of the cases were rated fair or poor, and in 31 per cent, good or excellent. [ED. NOTE: There are of course many factors to be considered which may influence end results in a series of this type. In some clinics fusion was done only in cases in which the condition was severe, and in others mild curves were fused. The age at which correction is done must also be considered. It is interesting to note that of the group treated by the Risser method between the ages of 12 and 15, 50 per cent showed excellent or good results

at the age of 12; 43 per cent, at the age of 13; 40 per cent, at the age of 14, and 50 per cent, at age 15, whereas for the total group only 31 per cent showed good or excellent results.]

The conclusions of this study are as follows:

1. Practically none of the patients with scoliosis are cured, if correction of lateral deviation is a criterion.

2. In approximately 60 per cent of those treated by exercises the deformity increased and in 40 per cent it remained unchanged.

3. Correction without fusion resulted in complete loss of correction after support was discontinued, in the majority of instances.

4. Correction by the turnbuckle jacket and subsequent fusion has yielded better results in this series than have other types of treatment.

[ED. NOTE: This report indicates the need for a great deal more work on the problem of the treatment of scoliosis. As pointed out in this report, the cosmetic deformity was the major problem, and the results of treatment were poor considering the entire group, at least from a cosmetic point of view. This brings out the point that the only real cosmetic improvement is obtained by correction and fusion. It seems, therefore, that from this point of view the correction and fusion must be done fairly early. It should also be mentioned that in a large percentage of cases the fusion is done to prevent further progress of the curve. If the curve is increasing when fusion is done, more has been obtained than mere cosmetic improvement of the existing curve. In considering the end results in the cases in which fusion was not done, one must take into account the fact that in a great many cases there is no increase and no operation is required. There is more and more evidence to support the view that either no treatment is needed or correction and fusion are indicated. Undoubtedly better cosmetic results and a greater percentage of correction could be obtained, and maintained, if all of the cases in which fusion is done were selected from cases in which the condition is relatively mild. The question must be raised, however, whether a large percentage of the patients could not do just as well without fusion and without any treatment.]

McElvenny<sup>545</sup> discusses the principles underlying the treatment of scoliosis. He attempts to explain the theory of this method of treatment by assuming a simple dorsal curve and trying to explain the development and treatment of this curve. In preparing this paper the author has made free use of the material offered in the fundamental articles by Ferguson and by Butte. He reviews the generally accepted principles of careful follow-up during the growth period and discusses the indications for operation and selection of patients for operation.

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545. McElvenny, R. T.: Principles Underlying Treatment of Scoliosis by Wedging Jacket, Surg., Gynec. & Obst. 72:228-236 (Feb.) 1941.

The author discusses the principles of correction and selection of the primary curve and the fusion area. Numerous illustrations to point out the primary curve, the marker film, the pelvic tilt roentgenogram and the selection of the primary curve are shown. Diagrams are used to illustrate the primary curve, the fusion area and the method of avoiding overcorrection of the primary curve or fusion of too long an area. [ED. NOTE: This is an excellent article on the subject of scoliosis and is worth reviewing by any one interested in the problem of scoliosis. It helps to explain some of the more complicated problems involved in the treatment of scoliosis, especially of this one particular type of simple curve. It is perhaps worth mentioning, however, for the benefit of those who have not treated a great many patients with scoliosis, that there are some cases in which there appears to be a typical single right dorsal curve and in which the lumbar curve may not be completely correctible. In some of these cases even though the principles outlined in this article are followed, it is possible for the so-called secondary or compensatory curve below the primary curve to develop the same characteristics as the primary curve, the result being what probably was originally a double primary curve and the lower curve increasing although the upper one was fused. The lower curve may continue to increase in the lumbar area as the patient grows although the dorsal curve has not been overcorrected at the time of operation and has shown no increase for a year or more later. This type of curve represents a difficult problem, especially in those patients treated in the younger age group in which there are several years of growth and possibility of increase in the so-called secondary curve even though the primary curve has been corrected and not overcorrected. The principles described in this article should be reviewed in the original article; they cannot be adequately abstracted without the illustrations and complete discussion. This is an excellent article.]

Steindler <sup>546</sup> points out that the treatment of scoliosis is a compromise, since complete automatic muscle control stability and mobility can be accomplished in only rare instances. The author believes that this compromise is acceptable for three reasons:

The important factor in the deformity is not the curve itself, but rather the loss of posture which it involves—the lack of alignment between the head, shoulders and pelvis—so even if it is not possible to restore the anatomical form of the column, it is possible in a majority of cases to approach a normal posture. We call this the realignment of the spine by compensation.

2. When this passive realignment is once obtained, the musculature can in a great many cases be adequately developed to maintain actively the posture so regained, even though the mobility of the spine has been greatly reduced by the scoliosis.

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546. Steindler, A.: *Conservative Compensation-Derotation Treatment of Scoliosis*, J. Bone & Joint Surg. 23:67-80 (Jan.) 1941.

3. In the absence of adequate musculature, the entire mobility of the spine can be sacrificed by fusion, and the posture thus maintained passively.

In any event, restoration of alignment or posture is a necessary prerequisite. The question then is whether the two pre-requisites of successful conservative treatment—the degree of compensation necessary to restore posture or general trunk alignment and the degree of muscle function required to maintain it actively are available.

The cases of scoliosis are divided into five groups:

1. Those in which realinement or compensation occur spontaneously.
2. Those in which adequate compensation can be accomplished by conservative means.
3. Those in which adequate compensation can be maintained and in which adequate muscle power can be developed but in which because of marked adaptive or congenital osseous changes and in spite of good musculature compensation is likely to break down again.
4. Those in which alinement is possible, but no adequate muscle tone can be obtained. This includes most cases of paralysis. The spines in these cases also should probably be fused.
5. Those which cannot be adequately realined because of severe structural deformity.

The compensation-derotation treatment is described, and the indications and the contraindications for treatment are pointed out. The conclusions are as follows:

1. Compensation of the scoliosis is a necessary prerequisite for maintenance of correction and posture.
2. The combined compensation-derotation method is adequate to obtain compensation in suitable cases and leads to definite maintenance of posture.
3. The rotary deformity of the thoracic spine cannot be corrected at present. Attempts to correct the thoracic deformity by rotation to the concave side are preposterous. The thorax is already rotated to the concave side in relation to the spinal column, and such attempts only make the situation worse.
4. Derotation is directed toward the lumbar and cervicothoracic sections of the spine, and, by limbering up these sections, aids in the development of adequate counter curves.
5. If the compensation can be accomplished without forcible cast correction, and provided muscle development is adequate, the spine need not be fused. However, if the compensation must be forced by a cast, fusion will become necessary to hold the correction obtained.
6. Failure must be expected, with or without fusion, when compensation is lost or not obtained. Only a few cases at the end of the growth period hold the correction when decompensated.
7. Failure must also be expected in the absence of adequate muscle development, unless fusion is performed.
8. Compensation-derotation plus adequate muscle development promises success in the great majority of all non-paralytic cases.
9. Adequate compensation-derotation plus fusion in the presence of inadequate musculature, likewise, holds out promise of success in all paralytic and many congenital cases.



[ED. NOTE: Any curvature of the spine must have compensatory curves for adequate alinement of the trunk. These compensatory curves will develop in any patient without treatment of any kind. An increasing number of orthopedic surgeons and physical therapists believe that symmetric postural exercises will obtain this necessary compensation, and as yet there has been no study to show whether or not the compensation-derotation treatment offers any better results than the routine symmetric postural exercises. It is believed that routine symmetric postural exercises will improve the posture, increase vital capacity and improve the patient's general appearance and general health. However, it is doubtful whether any of these conservative treatments have any significant effect on the progress of the curvature. Exercises to strengthen the trunk muscles naturally help the posture and prevent back fatigue. In considering the problem of scoliosis there is increasing evidence that the majority of patients need little if any treatment except observation to determine whether there is any increase in the curvature or correction and spinal fusion if the curvature is severe or progressing. There are of course other indications for operation, such as pain, cosmetic appearance, instability (especially in cases of poliomyelitis).]

Vom Saal<sup>547</sup> reviews the management of scoliosis but discusses mainly the operative treatment which is used in most clinics. He discusses also the causation of scoliosis and apparently believes that poliomyelitis scoliosis "may be caused by either back, abdominal, hip or shoulder girdle paralysis." In the discussion of the treatment of scoliosis the author states that "if the patient is 15 or 16 years old a comparison of her height with that of other members of the family suggests that she has about obtained her growth, simple support is all that is necessary." [ED. NOTE: The author implies that the progress of idiopathic scoliosis depends on increase in growth, and this is doubtful in view of recent studies. It is also questionable whether any support is necessary at all for patients with idiopathic scoliosis beyond the age of 16. Also, as noted elsewhere in this review, it is difficult to see how paralysis of the shoulder girdle muscles alone can cause scoliosis, except perhaps occasionally a mild functional type which needs no treatment.]

Cohen<sup>548</sup> reports an anatomic study of the relevant section of the vertebral column of a 10½ year old girl who had undergone a Hibbs spine fusion for scoliosis. The second stage spine fusion had been completed seven and one-half months prior to death, and the exact cause of death was not known except that at autopsy marked gastric dilatation

547. vom Saal, F.: Management of Scoliosis, *Am. J. Surg.* **52**:433-442 (June) 1941.

548. Cohen, L. J.: Anatomic Findings Following Hibbs' Spine Fusion for Idiopathic Scoliosis, *Bull. Hosp. Joint Dis.* **2**:114-118 (July) 1941.

was found. The author discusses this problem and quotes Lehman, who reported cases of more or less pronounced ileus, one with a fatal issue, occurring after fracture of the vertebra, the pelvis or the ribs. In Lehman's cases the paralytic ileus always occurred soon after the injury. Cohen's study showed that all of the vertebral joints were not completely obliterated, yet there was sufficient new bone formation between the laminae to indicate a successful fusion and the essential maintenance of the correction. [ED. NOTE: It is interesting to note that this patient had a solid fusion seven and one-half months postoperatively, and yet the small articular facets were not all solidly fused. This tends to bear out the opinion of many who believe that fusion of the articular facets is not necessary for a solid spinal fusion. However, the significance of the facets in this particular case might be questioned in view of the fact that the child was 10½ years of age and would normally be expected to have a fairly solid fusion. This is one of the few pathologic reports on the study of spines fused for idiopathic scoliosis by the Hibbs method.]

Ruhlin and Albert<sup>549</sup> report 7 cases of scoliosis complicated by spinal cord involvement selected from a series of 2,000 cases of scoliosis of all types, and their conclusions are as follows:

1. The level of the apex of the curve shows no correlation with the distribution of the neurological changes.

2. All motor changes are of the spastic type.

3. There is no definite sequence in the appearance of the sensory or motor manifestations.

4. Conservative therapy shows little, if any, permanent improvement in the neurological status; therefore, laminectomy should be performed if a short period of conservative treatment fails to relieve the signs and symptoms present, or if the neurological signs increase, whether the sensory or motor changes are in precedence.

5. Laminectomy incisions should be drained.

6. In this series progression of signs and symptoms following laminectomy developed in all patients, but receded after a variable period, except in case 3. This patient did not regain function.

7. Laminectomy offers the best prognosis in case of scoliosis with signs of compression, despite the fact that torsion and tension are the etiological factors of these signs.

8. It is desirable to combine fusion with laminectomy when the patient's condition will stand this added operative procedure. The fusion should extend from horizontal vertebra to horizontal vertebra. The combined method of Steindler is a rapid procedure which has proved satisfactory. There may be an increase in the curve if solid fusion is done before the end of the period of rapid growth.

[ED. NOTE: This is an interesting series of cases representing one of the rarer complications of scoliosis. In several large clinics of 2,000

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549. Ruhlin, C. W., and Albert, S. M.: *Scoliosis Complicated by Spinal Cord Involvement*, J. Bone & Joint Surg. 23:877-886 (Oct.) 1941.

or more cases, few, if any, cases of spinal cord involvement have been noted. The condition is fortunately rare. It should be noted that the authors state that "there may be an increase in the curve if solid fusion is done before the end of the period of rapid growth." It is generally believed that if the primary curve is solidly fused between parallel lines there can be no increase even during the period of rapid growth unless there is some failure within the fusion area.]

*Vertebral Epiphysitis.*—Hodgen and Frantz<sup>550</sup> discuss the problem of juvenile kyphosis. They discuss briefly the clinical picture, speculations as to causation, pathologic nature and treatment and present a study of 50 cases. The most frequent age of onset was between 10 and 11 years. Contrary to some observers, the incidence was found to be greater in girls, being 78 per cent. They found the condition twice as frequent in the thin children of the asthenic constitution as in the short stocky pyknic persons. They describe the typical picture as generally consisting of a rounded back with limited mobility, a relaxed abdomen, increased lordosis and hyperextension at the knees. They state that in their experience they have not seen the severe rounded kyphos pictured in foreign publications. They also point out that the chest is more or less flat and plays a minor part in breathing.

[ED. NOTE: It should be pointed out that round back must be divided into functional and structural the same as lateral deviations of the spine or scoliosis. Patients with round back due to poor posture tend to have a flat chest and round shoulders whereas patients with actual wedging of the vertebral bodies usually have a definite increase in the anterior posterior diameter of the chest, and the chest is frequently prominent anteriorly. In addition the structural round back shows marked convexity in the area of involvement on forward bending, whereas the round back due to poor posture tends to disappear and there is a long symmetric curve of the entire spine on forward bending, the spine usually being flexible.]

The authors discuss the conservative treatment of juvenile kyphosis but do not discuss the operative treatment.

[ED. NOTE: It should be pointed out that as in scoliosis, probably the only treatment which will give satisfactory cosmetic results in some cases is correction and fusion before the deformity becomes too severe. One great difficulty in the problem of adolescent round back is the fact that there is a slow and insidious onset; by the time the child and the parents or the surgeon decide on operation there has already been considerable wedging of the involved vertebrae. This whole subject needs considerable further study in order to determine the cases in

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550. Hodgen, J. T., and Frantz, C. H.: Juvenile Kyphosis, Surg., Gynec. & Obst. 72:798-806 (April) 1941.

which increase is definitely to be expected and those in which spinal fusion should be done in the local area of vertebral wedging. Unlike scoliosis, round back usually involves only a relatively small number of vertebrae (sometimes only three to five vertebrae), and this whole area can be fused at one operation and without the elaborate correction involved in treating scoliosis if fusion is done sufficiently early. The spinal fusion operation can be expected to arrest the increase in kyphosis, but the cosmetic improvement is frequently relatively slight as the operation is so frequently done as a last resort at a time when the cosmetic appearance is already bad and correction of a dorsalis kyphosis is difficult.]

Adelstein <sup>551</sup> reports a case of extradural spinal cyst associated with kyphosis dorsalis juvenilis and presents 16 other cases collected from the literature. He believes that the clinical picture of an adolescent with progressive paraplegia together with erosion of the vertebral bodies in the midthoracic region as seen in kyphosis dorsalis juvenilis is pathognomonic of an extradural spinal cyst. He feels that all patients with kyphosis dorsalis juvenilis should be carefully examined for evidence of compression of the spinal cord and for roentgen evidence of enlargement of the spinal canal. He believes that the wedging seen in this condition with extradural cyst results from venous stasis secondary to the presence of the cyst. He points out that the causation of kyphosis dorsalis juvenilis unassociated with an extradural cyst is unknown. He believes that early surgical intervention with removal of the intraspinal cyst usually results in complete cure with relief of all signs of compression of the spinal cord and prompt arrest of the kyphotic deformity. [ED. NOTE: This is a good paper, and while the subject has been previously presented, it brings to attention again this interesting relation between kyphosis dorsalis juvenilis and spinal extradural cyst. There are undoubtedly many cases of kyphosis dorsalis juvenilis associated with spinal extradural cyst in which the presence of the extradural cyst is overlooked. As in other lesions of the spine there are probably several or many causative factors which may produce the same resulting changes in the vertebral bodies and the same relative roentgen picture. This perhaps should be mentioned since the paper is likely to imply that the spinal extradural cyst is common in kyphosis dorsalis juvenilis when actually it is one of the rare causes for this condition. This paper should stimulate further study on the subject of kyphosis dorsalis juvenilis about which so little is known at present.]

Schaefer and Purcell <sup>543</sup> express the opinion that vertebral epiphysitis or juvenile osteochondritis is due to hypothyroidism. They suggest

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551. Adelstein, L. J.: Spinal Extradural Cyst Associated with Kyphosis Dorsalis Juvenilis, *J. Bone & Joint Surg.* **23**:93-101 (Jan.) 1941.

treatment with thyroid and apparently do not differentiate between idiopathic scoliosis and adolescent round back. [ED. NOTE: While some patients with juvenile osteochondritis may have a thyroid deficiency and while thyroid deficiency may be a factor in some cases, there is still insufficient evidence to conclude that thyroid deficiency is a major cause of this condition.]

Corsellas and Baila<sup>552</sup> discuss the problem of vertebral epiphysitis. They present a résumé of the literature and feel that the description of Calvé does not fit in with the symptoms. They prefer to call this lesion epiphysitis. They feel that this condition must be classified in the group of bone dystrophies of puberty and adolescence along with the other forms of epiphysitis, and they think that late rickets, aseptic necrosis and small repeated trauma in persons with endocrine insufficiency are the contributing factors in this disease. The authors emphasize the importance of differential diagnosis by roentgen examination between epiphysitis and early Pott's disease of the spine. They also present the differential diagnosis between epiphysitis and Marie-Strümpell arthritis and typhoid spondylitis. The authors consider the prognosis fairly good and suggest rest in bed and occasionally plaster beds for treatment. They also advise the giving of vitamin D and calcium as well as postural exercises. This article is illustrated with the patients at different ages, showing the characteristic roentgen appearance of the epiphysitis and the differentiation from Pott's disease and other conditions.

*Osteochondritis of the Vertebra.*—Kuhlman<sup>553</sup> briefly reviews the literature on vertebra plana. This condition was first described by Calvé as noted in children and similar in character to Legg-Calvé-Perthes disease of the femur and other osteochondritides. Since that time many different names have been applied, especially vertebral epiphysitis, juvenile kyphosis, osteochondritis deformans and osteochondritis of the vertebra. The disease is usually found in children 2 to 15 years of age, the greatest incidence being between 5 to 10 years. The author points out that the disease starts with slight narrowing of the vertebral body and an increase in the widths of the intervertebral disks with the latter not eroded or destroyed. The involvement is usually limited to one segment, although occasionally more than one vertebra shows involvement. The progress is usually rapid with flattening of the vertebra and continues until only a thin disk of bone remains. At this time the intervertebral disks adjacent are much wider than normal. The density of bone is usually well maintained, and at the end, when the

552. Corsellas, M. F., and Baila, A. E.: Vertebral Epiphysitis, *Prensa méd. argent.* **28**:598-611 (March 12) 1941.

553. Kuhlman, F. Y.: Vertebra Plana (Calvé): Report of Two Cases, *Am. J. Roentgenol.* **46**:203-206 (Aug.) 1941.

collapse is complete, the density is greater than normal. Regeneration of the body is said to take place without much new bone formation in the adjacent structures.

In some instances the contour of the vertebra has been reported to be completely restored in a year's time. Diagnosis rests on roentgen findings; in most cases the clinical diagnosis is tuberculosis of the spine. However, the roentgen picture is characteristic. The density of bone is normal or increased instead of decreased as in cases of tuberculosis. The intervertebral disks are wider than normal and are not involved, whereas in cases of tuberculosis the disks are usually the point of early attack and are destroyed. The regeneration is reported to be more rapid than in cases of tuberculous disease and more uniform in character; it occurs without fusion of the involved segments with the adjacent vertebrae. The author reports 2 cases; in one the patient was a girl aged 5 years and in the other a boy aged 8. Trivial trauma to the back preceded the onset of symptoms in both cases; the significance of this is not certain. There was a history of acute infectious disease prior to onset of symptoms in both cases; the significance of this is likewise uncertain. It is conceivable that trauma or infection or both were instrumental in introducing embolic or thrombotic phenomena in the nutrient vessels of the vertebra and that this in turn led to necrosis of the bone and collapse of the involved segment.

[ED. NOTE: This is a good article and is well written. While it does not report any new condition, it again calls to attention a condition which is rare and which is usually confused with tuberculosis.]

*Dorsolumbar Syndrome.*—Slobe<sup>554</sup> discusses the dorsolumbar syndrome with special reference to referred pain. He states that

The frequency with which fibrositis occurs in the mid-back (dorso-lumbar region) is not sufficiently recognized. Such pathology quite commonly gives rise to characteristic referred pain and the combination may well be called the "dorsolumbar syndrome" to distinguish it from the frequent "sciatic syndrome" associated with low-back involvements.

The literature is replete with articles dealing with low-back pain and the sciatic syndrome but relatively few articles emphasize the frequency of dorso-lumbar involvement.

The author uses the term "fibrositis" for lack of a better term to include myositis, fascitis, periarthrititis, arthritis and other conditions, in fact any inflammatory or degenerative disease involving the muscles, the fascia ligaments, the periosteal insertions, the joints and the nerve sheaths. The author presents 4 cases to illustrate his point. He points out that tenderness of the testicle, the inguinal canal, the lower portion of the abdomen, the upper part of the thigh and the superolateral por-

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554. Slobe, F. W.: Dorsolumbar Syndrome with Special Reference to Referred Pain, Illinois M. J. 80:332-336 (Oct.) 1941.

tion of the buttock usually can be elicited, sometimes largely confined to one area, sometimes to several and sometimes over all these areas. He states that this association of severe pain with tenderness causes mistaken diagnoses of incarcerated hernia, appendicitis, renal colic, pelvic disease and other conditions, causing needless operations to be performed. He suggests the use of local anesthesia as a diagnostic as well as therapeutic aid.

[ED. NOTE: This article falls into the group reviewed in "Progress in Orthopedic Surgery for 1940" which dealt with the so-called viscerospinal syndrome, spinal appendicitis and other conditions. It is perhaps worth while to stress the importance of these cases of referred pain.]

*Spinal Root Pain.*—Eaton<sup>555</sup> describes the outstanding characteristics of root pain which are valuable in differential diagnosis and emphasizes these characteristics by considering the mechanics of the production of the pain. The author discusses the various kinds of root pain. He believes that dilatation of the veins in the epidural space with coughing, sneezing and straining dislocates the dura toward the spinal cord, stretches the enveloped nerve roots and thus produces pain. He points out that it has generally been assumed that such intensification of pain results from an increase in pressure from the spinal fluid. However, he notes that jugular compression rarely intensifies root pain unless the pain is due to a tumor of the spinal cord which produces dynamic subarachnoid block. He has made several tests with lumbar puncture and jugular compression to illustrate his point that increasing the pressure of the spinal fluid alone does not intensify root pain. He states that increasing the size of the epidural space with consequent displacement of the dura toward the spinal cord is the factor responsible for intensification of the pain by virtue of traction on the diseased nerve roots. He also explains root pain at night by spontaneous elongation of the spinal column during sleep. He attempts to prove this by measurement of several patients at the various periods of activity and sleep. One patient increased 60 mm. in height after sleeping.

*Articular Process Fissures.*—Oppenheimer<sup>556</sup> reports 4 cases of longitudinal fissures in the vertebral articular processes. He points out that

Radiolucent gaps in the neural arch and its processes are known to be due to persistence of cartilaginous union and failure of bony union between parts which arise from distinct centers of ossification. Most of these so-called fissures are in the laminae, in the isthmus between the superior and inferior articular processes,

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555. Eaton, L. M.: Pain Caused by Disease Involving Sensory Nerve Roots (Root Pain): Its Characteristics and Mechanics of Its Production, *J. A. M. A.* **117**:1435-1439 (Oct. 25) 1941.

556. Oppenheimer, A.: Longitudinal Fissures in Vertebral Articular Processes, *J. Bone & Joint Surg.* **23**:280-282 (April) 1941.

and at the tip of the inferior articular processes of the lumbar vertebrae. An additional fissure, apparently not yet recorded, was found in four persons. In each of them, it was associated with gaps at the tips of the articular process and, in one patient, with gaps in both the isthmus and the lamina of the same vertebra. It extended from the region of the isthmus along the longitudinal axis of the articular process down to the gap at its tip, the two fissures standing at right angles. . . . In all the cases the outlines of the longitudinal fissure were irregularly serrated, which suggested a fracture line. None of the patients, however, remembered having incurred an injury, and there were no signs or symptoms whatever referable to the spine. The gaps were discovered accidentally in roentgenograms of the digestive or urinary tract. Since there is only one center of ossification for the main part of each articular process, according to present knowledge, it would seem difficult to account for the longitudinal gap by a developmental failure of bony union. However, the constant combination with a second gap known to be due to such a failure, together with the absence of a history or clinical signs of trauma, is in favor of a developmental anomaly.

He points out also that longitudinal fissures are rare and that their incidence in his observations were as low as that of aplasia of articular processes (about 0.09 per cent of all spines examined). The significance of these longitudinal gaps seems to lie in the fact that they look like fracture lines. He states that fractures of the articular processes are rare, most of them being combined with fractures of other parts of the vertebrae. He observed only 3 cases of fracture of an articular process without other vertebral lesions; in each of them the clinical signs and symptoms were definite, and the trauma had been severe. In 2 of them there was radicular neuritis with atrophy of the corresponding muscles and bone, and in all cases the mobility of the spinal section involved was greatly diminished. The fact that a longitudinal fissure resembling a fracture line may exist in the complete absence of clinical manifestations may be worth recording, since increasing importance is given to roentgen findings in deciding on questions of treatment and of compensation after some relatively slight injury.

[ED. NOTE: This is an interesting report and should be kept in mind by orthopedic surgeons in connection with compensation or medico-legal cases.]

*Anatomy and Anatomic Variations of the Spine and Thorax.*—Fuchs<sup>557</sup> presents an interesting study of the thoracic vertebrae with excellent illustrations of photographs of the individual vertebral bodies with comparable roentgenograms of these bodies in the varying positions. He identifies the various outstanding points on the roentgenograms and the photographs for clear interpretation of the roentgen shadows. He also points out the various anomalies, the landmarks to be noted and the technic for obtaining best visualization of the thoracic

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<sup>557</sup> Fuchs, A. W.: Thoracic Vertebrae, Radiog. & Clin. Photog. **17**:2-13, 1941.



vertebrae. [ED. NOTE: This article has beautiful illustrations and could well be included in any bibliography on the study of anatomy, anomalies and other orthopedic problems or roentgen technic. It is probably of more interest to roentgen technicians or to any one making a special study of any condition involving the thoracic spine, including scoliosis.]

Zadek<sup>558</sup> reports a tackhammer deformity of the sternoxiphoid cartilages causing gastrointestinal symptoms relieved by excision. The author states that he has been unable to find a record of a similar condition in the literature. The patient aged 39 complained of pain in the pit of his stomach. It occurred six months before examination without any history of previous injury. The pain was especially troublesome when the patient was in bed. It was acute when the patient was supine, and the most comfortable position was lying on the left side. When on occasions he had lifted a heavy object, the pain was so sharp that it caused him to drop the object. The condition progressed so that he could not eat normally, and he complained that everything seemed to catch in the pit of his stomach. The patient lost 35 pounds (15.9 Kg.) within six months. On examination there was no rigidity or spasm of the abdominal muscles. The patient had an unusually long xiphoid cartilage which was nearly 3 inches (7.6 cm.) in length. It was freely movable, and roentgenograms showed the fishtail appearance of the xiphoid process. The xiphoid process was removed at operation. It was found that the tip of the deformed process was cartilaginous and that the recti muscles seemed to catch as they were moved over these prongs laterally and medially. [ED. NOTE: This is an unusual deformity of the chest and is apparently rare or at least not frequently observed in orthopedic cases.]

*Involvement of Ribs and Rib Cartilages.*—Holmes<sup>559</sup> reports a study of slipping rib cartilage syndrome. He reviews the literature on this subject. This condition was first reported by Cyriax. The author points out that because of the failure to recognize this syndrome needless laparotomies are performed and prolonged suffering and incapacity from an easily curable condition are often permitted. Moreover there does not appear to be any clear conception of the development of this deformity. He points out that the deformity involves the cartilages of the lower ribs, notably the eighth, the ninth and the tenth, by displacement of fracture fragments or dislocation of the cartilage or more often by curling the end of the loosened cartilage so that on respiration or

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558. Zadek, I.: Tack Hammer Deformity of Sternal Xiphoid Cartilage Causing Gastrointestinal Symptoms Relieved by Excision, *Bull. Hosp. Joint Dis.* 2:111-113 (July) 1941.

559. Holmes, J. F.: Study of Slipping-Rib-Cartilage Syndrome, *New England J. Med.* 224:928-932 (May 29) 1941.

motion the deformed cartilage end slips over or rubs against the inside of the rib above with a click which is felt by the patient and in some cases is accompanied by severe and incapacitating pain. The author reviews 33 cases, 15 already reported and 18 new cases. He concludes that the slipping rib cartilage occurs more frequently from indirect than from direct trauma. The author states that the diagnosis of slipping rib cartilage is made from the complaint of pain, usually in the rib border, and by digital examination with the patient relaxed and supine with the knees flexed, in which position the abnormally movable rib cartilage with its associated click and pain can be demonstrated. Limitation of chest expansion as demonstrated by measurement is also a suggestive diagnostic feature. The treatment of this condition as reported in the literature has largely consisted in excision of the rib cartilage involved and has been followed by immediate and complete relief of symptoms. The author concludes that slipping rib cartilage is an entity presenting a classical clinical picture. It often produces irksome and incapacitating symptoms. Following excision of the offending rib cartilage or cartilages, immediate and permanent cure was obtained in every case.

*Hemangioma of the Vertebrae.*—Ghormley and Adson<sup>560</sup> point out that vertebral hemangioma is a definitely recognizable condition which may not cause symptoms. However, the symptoms of some patients, particularly the younger ones, may be marked even to the development of complete paraplegia. In such cases laminectomy with decompression followed by roentgen therapy offers the best possibility of relief. For patients in whom paraplegia is not present but in whom there is evidence of compression of the spinal cord or local symptoms, roentgen therapy is the treatment of choice. Supportive corsets or braces should be used whenever they are indicated, e. g. for patients who have the static type of pain or sufficient involvement of the vertebra by the hemangioma to cause pathologic compression fracture. This complication, however, is rarely noted. The authors illustrate the roentgen picture of hemangioma of the vertebra and report a series of 39 patients, of whom 27, or 69 per cent, were female, 12, or 31 per cent, were male. One of the striking facts brought out in this review is the lower average age of patients who have had symptoms. The authors divide the condition into four types: (1) hemangioma with paraplegia; (2) hemangioma with symptoms of compression of the spinal cord but without paraplegia; (3) hemangioma with local symptoms and signs but without evidence of compression of the spinal cord; (4) hemangioma without any symptoms or signs. They describe the roentgen findings, pointing out that in the early phase of the disease there are areas of hypertrophy of the

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560. Ghormley, R. K., and Adson, A. W.: Hemangioma of Vertebrae, J. Bone & Joint Surg. 23:887-895 (Oct.) 1941.

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558. Zadek, I.: Tack Hammer Deformity of Sternal Xiphoid Cartilage Causing Gastrointestinal Symptoms Relieved by Excision, *Bull. Hosp. Joint Dis.* 2:111-113 (July) 1941.

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560. Ghormley, R. K., and Adson, A. W.: Hemangioma of Vertebrae, J. Bone & Joint Surg. 23:887-895 (Oct.) 1941.

pedicle and the lamina, enlargement of the intertrabecular spaces and absorption of trabeculae in the body with thickening of other trabeculae, thus giving the appearance of channels situated between or interwoven among the trabeculae. They state:

In the more advanced stages of the disease, a ballooning process takes place, the body of the vertebra is flattened, and the walls have a tendency to bulge. This process accounts for the narrowing of the spinal canal. In a few instances a pathological fracture has occurred, which accounts for the kyphosis or scoliosis.

[ED. NOTE: This is a good article and summarizes the present knowledge of hemangioma of the vertebrae, presenting the indications for treatment and the treatment to be used.]

*Intervertebral Disks of the Cervical Part of the Spine.*—Stone, Arieff, Kaplan and Brown<sup>561</sup> present a case of multiple protrusions of the fifth and sixth cervical intervertebral disks.

. . . The onset was sudden like that of an acute inflammatory lesion of the lower cervical region of the spinal cord. In four months a quadriparesis (left lower extremity completely paralyzed), dissociation of sensibility, atrophy of the hand muscles and a Horner's syndrome resulted. The findings of a complete spinal block, increased protein content of the spinal fluid and a questionable narrowing of the 6th cervical vertebrae were indications for neurosurgical exploration.

The authors state that protrusion or rupture of an intervertebral disk in the cervical region is not common and that multiple protrusions in this region are less common and may simulate a syndrome complex of acute inflammation, syringomyelia or spinal compression.

*Rupture of Muscles of the Abdominal Wall.*—Sileo<sup>562</sup> reports a case of spontaneous rupture of the external and internal oblique muscles with hematoma of the abdominal wall. He points out that the diagnosis of spontaneous hemorrhage into the abdominal muscles is difficult to make. Recognition of the condition is made difficult because palpation usually gives no evidence of the intramuscular location of the tumor. When the hematoma is removed, the condition usually subsides rapidly. In view of the difficulty and the uncertainty of the diagnosis and the doubtful results of conservative therapy, operation is recommended for use in all cases. Conservative treatment should be employed only when the insignificance of the findings does not warrant surgical intervention. [ED. NOTE: Probably most of these patients would come under the care of the general surgeon rather than of the orthopedic surgeon.]

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561. Stone, T. T.; Arieff, A. J.; Kaplan, L. A., and Brown, C.: Protrusion of Two Intervertebral Disks in Cervical Region: Report of Case, *J. Nerv. & Ment. Dis.* **93**:719-722 (June) 1941.

562. Sileo, J. A.: Spontaneous Rupture of External and Internal Oblique with Hematoma of Abdominal Wall, *Bull. New York M. Coll., Flower & Fifth Ave. Hosp.* **4**:55-58 (June) 1941.

*Odontoid Process.*—Wade<sup>563</sup> reports a case of backward and lateral displacement of the odontoid process which simulated a case of platybasia. This is an unusual case as the injury occurred thirty years before death. It is an interesting report of the clinical and autopsy observations on a patient who had a persistent bilateral lesion of the pyramidal tract attributable to injury sustained thirty years before her death. It is of interest that the degenerative changes in the pyramidal tracts below the site of compression were greatest on the left side, even though the infarct was in the left internal capsule. The left side of the cord was in nearest proximity to the odontoid process. There had been a rupture of the transverse axis ligament with displacement of the odontoid process and compression of the cervical cord.

#### XIV. CONDITIONS INVOLVING THE HIP JOINT

*Osteochondritis of the Head of the Femur.*—There is still considerable disagreement as to the causation of osteochondritis. Traumatic, bacteriologic and endocrine factors have each received varying emphasis. The question is naturally one of extreme importance for the establishment of a rational basis of therapy. Two new articles which approach the subject from this standpoint have appeared in the literature of the past year. The first is an attempt to correlate Legg-Perthes disease, coxa vera, osteochondritis dissecans and other conditions under a single mechanistic theory; the other emphasizes hormonal deficiency.

Bozsan,<sup>564</sup> in a lengthy article in which he follows the historical development of the idea, states that osteochondritis dissecans of the femoral head, several forms of coxa vara, Legg-Perthes disease, slipping of the femoral epiphysis, ischiopubic and acetabular osteochondritis are all related and are the result of traumatic compression of cancellous bone. This conception of the pathogenesis is one which the author states will clear the prevailing confusion and facilitate the understanding of the grosser features of the whole group if given the key position it merits. The conception is an ingenious one supported by pathologic, radiologic and clinical material although perhaps somewhat lacking in experimental evidence. The author believes that the characteristic wedge-shaped areas of aseptic necrosis may be produced by a mechanism other than infarction, namely, by compression of spherically shaped portions of cancellous bone. Such compression of spherically shaped bodies causes damage

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563. Wade, L. J.: Pseudoplatybasia, Rupture of Transverse Ligament of Axis with Displacement of Odontoid Process and Compression of Cervical Cord, *J. Bone & Joint Surg.* **23**:37-43 (Jan.) 1941.

564. Bozsan, E.: Compression of Cancellous Bone: Principal Manifestations in Head and Neck of Femur; Treatment by Connecting Drill Channels, *Am. J. Surg.* **53**:567-618 (Sept.) 1941.

in an area which is wedge shaped on cross section but which in actuality corresponds to a cone the base of which lies at the site of the application of the force. The compression does not damage the entire substance of the cone but is most effective in its peripheral extent and produces within the compression pattern secondary component wedges. Each impact produces its own wedge, and the compression pattern varies with changes in the curvature of the surface and speed of force resulting in various combinations of superimposed patterns. These effects are illustrated by analogy with the bruising of an apple and by the roentgen appearance of osteochondritides.

On this conception the author bases his therapeutic principles which essentially consist of drilling the compression barrier to facilitate the healing process. The therapeutic results are illustrated by 23 cases of the group of diseases which he believes are due to this process.

The second article is that of Schaefer and Purcell,<sup>565</sup> who contend that the so-called juvenile chondroepiphysitis is due neither to an inflammatory process nor to vascular changes but is specifically due to hypothyroidism with consequent lack of tissue-differentiating factor. They suggest that the confusing terminology be done away with, and they propose with more certainty than present knowledge will perhaps warrant that the entire group be given the name osteochondral hypothyroidism. The authors' contention has been fully developed in a former study,<sup>566</sup> and the present article deals with results of treatment in a series of 27 cases with desiccated thyroid.

They divide hypothyroidism into primary and secondary types. By primary is meant a clinical disturbance in which no signs of dysfunction can be determined except those referable to the thyroid. The authors imply that in cases of secondary hypothyroidism the primary failure is of a gland other than the thyroid, such as the hypophysis, resulting in growth or sex disturbances together with the associated and determinable signs of thyroid deficiency. The authors' requirements for the diagnosis of hypothyroidism, either primary or secondary, are the usual ones, namely, clinical history, developmental delay, decreased basal metabolic rate below — 10 per cent, increased blood cholesterol above 200 mg. per hundred cubic centimeters of blood and the presence of chondroepiphysial changes.

Of the 27 cases reported, there were 2 of Legg-Perthes disease, 2 of slipped capital femoral epiphysis, 10 of Osgood-Schlatter disease, 6 of calcaneoapophysitis, 2 of Kohler's disease and 5 of epiphysitis of the

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565. Schaefer, R. L., and Purcell, F. H.: Juvenile Osteochondreal Hypothyroidism, *Am. J. Surg.* **54**:589-604 (Dec.) 1941.

566. Schaefer, R. L.; Strickroot, F. L., and Purcell, F. H.: Endocrine Implication of Juvenile Chondroepiphysitis, *J. A. M. A.* **112**:1917-1919 (May 13) 1939.

spine. The patients' ages ranged from 5 to 15 years, and the authors claim that all displayed definitely related symptoms and that the roentgen diagnoses were unbiased, being made by a cross section of capable roentgenologists. All patients received routinely desiccated thyroid in full therapeutic doses by mouth, and in addition those displaying other signs of endocrine dysfunction, such as delayed pubescence, were treated with chorionic gonadotropin. Obesity was corrected when present, and all patients were ambulatory. Orthopedic treatment is regarded as adjunctive. Only 1 patient with Osgood-Schlatter disease required immobilization for two weeks.

The authors feel that normal ossification of the epiphyses was hastened as indicated by subsequent roentgenograms and that clinical cure was effected more rapidly.

*Ischiopubic Osteochondritis.*—Steinsleger<sup>567</sup> reports 2 cases and Garcia and Nespolo<sup>568</sup> 3 cases of this condition. They all emphasize that differential diagnosis may be difficult. Steinsleger points to the value of a secondary roentgenogram taken a few months later which demonstrates reparative processes not seen in cysts or bone tumors. The condition may make its appearance between the fifth and the twelfth year, although the conjoint ramus usually closes at approximately the ninth or the tenth year, and this suggests that in some instances the closure is delayed by the pathologic process. The condition is of interest because it may give rise to vague hip symptoms which may lead to wrong diagnosis and radical treatment for a condition which is benign and which can be cured in a relatively short time by simple rest and recalcification therapy.

*Slipping of the Capital Femoral Epiphysis.*—Thrap-Meyer<sup>569</sup> reports that all of the literature which he has reviewed contains no mention of a single instance of slipping of the capital femoral epiphysis in several members of the same family or in more than one generation. He reports 1 case in which both the father and the son showed a slipping of the epiphysis of the head of the femur. He draws no conclusions from this case but suggests the theoretic possibility of a hereditary factor in the causation of this condition.

Forrester-Brown<sup>570</sup> reports the end results of conservative treatment of slipping of the upper femoral epiphysis. He emphasizes that the

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567. Steinsleger, M.: Ischiopubic Osteochondritis, Bol. Soc. de cir. de Rosario 7:485-491 (Nov.) 1940.

568. Garcia, A. L., and Nespolo, J. S.: Ischiopubic Osteochondritis: Cases, Semana méd. 1:1136-1141 (May 15) 1941.

569. Thrap-Meyer, H.: Epiphysiolysis Capitis Femoris in Two Generations: Casuistic Report, Acta orthop. Scandinav. 11:1-10, 1940.

570. Forrester-Brown, M.: Slipping of Upper Femoral Epiphysis: End Results After Conservative Treatment, J. Bone & Joint Surg. 23:256-262 (April) 1941.



object of treatment should be to obtain a joint the range of motion of which, however limited, is through the most valuable or important arcs rather than a perfect reduction as shown by roentgenograms with a flexed, abducted or adducted limb. There is usually a gradual increase in the range of motion over a period of years following conservative treatment, whereas patients treated by more radical measures often show good results at first with a gradual progression of stiffness over a long period.

Of the author's 22 patients, 19 showed definite endocrine abnormality, some with increased sugar tolerance. These patients were given thyroid, and some were given thyroid and injections of whole pituitary. Definite improvement was noted. The author feels that there is a frequent generalized and persistent softening of bone in these cases as demonstrated by the frequency of severe knock knee as a complication which is much aggravated through spasm of the adductor muscles of the thigh. The presence of knock knee is one of the factors which make treatment without abduction of the hip desirable.

Heavy traction was used as a preliminary in some of the writer's earlier cases, but the result proved disappointing, the only result being that the weights pulled the hip below its normal level in the acetabulum without effecting any change in the relation of the head to the neck.

The technic used was essentially that of Leadbetter, a general anesthetic being given in nearly all cases. An attempt is made to rotate the limb internally and extend it without losing the internal rotation. A normal amount of internal rotation is usually accomplished. A plaster spica cast is applied to maintain extension with a minimum of abduction. The foot is included in order to control the internal rotation. The patient is allowed up and about as soon as the cast is dried. The plaster fixation is maintained until definite trabeculation is seen to cross the epiphysial line.

Serial roentgenograms of these patients taken every few months for a period of years after manipulation show progressive reconstruction of the upper end of the femur by which the line of weight bearing is gradually deflected into normal lines with increased density of new trabeculae. In all cases full extension of the hip and internal rotation to neutral were maintained. In 1 case the internal rotation was increased beyond normal. All patients walked with a normal attitude, but all had some limitation of flexion. They were able to sit without discomfort. Nine of the 22 patients had limitation of abduction and adduction and of external rotation. Only 1 had a full range of motion in all directions.

In the author's opinion this simple method of treatment gives good functional hip joints, and the results compare favorably with those of methods which are more difficult to carry out and more dangerous to life and limb.

Howorth<sup>571</sup> reports the end results of 132 cases which were the subject of a communication eight years previously.<sup>572</sup> Half of the children were not of the endocrine type, but 65 per cent were definitely tall or overweight. Trauma of a sufficient degree to cause epiphysal displacement was rarely present.

Four stages of the disease are described. These are the preslipping, the slipping, the quiescent and the residual stage. The condition is quiescent when symptoms and signs have subsided and is residual when there is complete bony union at the epiphysal line. The author found the leukocyte count of the blood to be 10,000 to 12,000 in half of the cases without an increase of the polymorphonuclear percentage. The erythrocyte sedimentation rate, however, was above 10 mm. per hour in 90 per cent of the cases, and in 1 instance it was as high as 40 mm., the average being 25 mm. Downward displacement of the head is regarded by the author as more serious than posterior displacement, for limitation of motion and arthritic changes are more common. He states that circulatory changes in the head are rare unless the head has been separated from the neck by surgical means. Of the 70 patients operated on, 17 were in the preslipping stage. In the preslipping stage the capsule was usually found to be edematous and thickened and the periosteum and the synovial membrane to be thick, red, softened and vascular with a tendency toward pannus formation. Softening of the epiphysal disk could be discerned with the aid of an instrument. Cultures of the soft tissues and of the synovia were consistently negative.

In the slipping stage there was usually a fold of soft redundant synovial membrane in the posteroinferior angle, and pannus formation was usual. In no instance was there actual separation between the head and the neck, even in those cases in which opening was done immediately after slipping. A layer of firm, fibrous or cartilaginous tissue covered the exposed portion of the end of the neck and joined it to the cartilage of the head. Usually the distal part of the epiphysal disk was soft, but in later stages it was firm and sometimes solidly ossified. Callus of varying degrees of maturity filled the posteroinferior angle.

In the author's opinion the primary pathologic condition is synovitis of the hip during rapid growth which causes circulatory disturbances of the epiphysal disk which results in its decalcification and softening with subsequent slipping. The cause of the synovitis is not proved, though the clinical and the pathologic picture and the alternating sedimentation rates suggest infection. The negative cultures are explained as being possibly due to difficulties of culturing the organisms or the virus involved.

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571. Howorth, M. B.: Slipping of Upper Femoral Epiphysis, Surg., Gynec. & Obst. **73**:723-732 (Nov.) 1941.

572. Ferguson, A. B., and Howorth, M. B.: Slipping of Upper Femoral Epiphysis: Study of Seventy Cases, J. A. M. A. **97**:1867-1872 (Dec. 19) 1931.

In the quiescent and residual stages correction of the deformity by subtrochanteric osteotomy is preferred because there is less likelihood of secondary damage to the head. As he stated in the previous study, closed reduction by manipulation was unsatisfactory, for in the majority of cases permanent limitation of motion following prolonged immobilization was the rule. Reduction of the epiphysis by strong traction was attempted early in 7 cases. The downward displacement was corrected in most of them, although usually the rotation could not be overcome. All of the epiphysial disks healed well, but the cortex of the head was irregularly ossified and the joint space thinned. Final motion was good in only 1 case, fair in 1 and poor in the remainder. Howorth believes that the poor results are due to injury of the capsule and of the circulation by traction. Eleven open reductions, 6 of them osteotomies through the proximal end of the neck, were reported in the first series. These were performed some weeks after slipping. In the later series 17 open reductions were done through the epiphysial disk. Eleven of the patients were immobilized in plaster for ten to twelve weeks. There were only 2 who showed good results, both having had preliminary rest with light traction. There were 2 complete failures, one requiring fusion and the other arthroplasty at a later date. On the remaining 6 who had open reduction, internal fixation with the Smith-Petersen nail and the Lippman screw was done also. The results were far better, in 2 cases being good, in 3, fair, and in 1, poor. Follow-up averaged two and one-half years. However, of a total of 28 hips on which open reduction was performed, 5 showed good results and 9 showed fair results, leaving 14, or 50 per cent, showing poor results. Internal fixation with early active motion is preferable when open reductions are done. A preliminary period of rest in bed with light traction is advantageous.

The author at first felt that if the patient were kept in bed in the preslipping stage so as to avoid weight bearing the slipping would not progress and the lesions would heal. However, in patients who had been kept in bed for several months, the slipping occurred suddenly as soon as weight bearing was resumed.

The drilling operation was later used in 17 cases in an attempt to produce premature union in the preslipping stage and in 23 cases with slight displacement. The Smith-Petersen approach was used. Several holes were drilled, curetted or gouged from the neck across the epiphysial disk and into the head. Long and thin slivers of bone taken from the ilium were inserted into these holes. Owing to technical errors there were 3 initial failures in a total of 40 cases. In 2 cases bone pegs were not used, and in these union was slow. In the remaining 35 hips, however, the lesion healed in from eight to twelve weeks, and bony union was complete within six to twelve months.

*Aseptic Necrosis.*—Banks<sup>573</sup> reports 9 cases of aseptic necrosis of the femoral head following traumatic dislocation of the hip. The reappearance of symptoms after an early period of apparent recovery is now known to be due to aseptic necrosis of the head of the femur; this results from a disruption of a major portion of the blood supply of the femoral head at the time of the dislocation. The author emphasizes that while death of the femoral head occurs shortly after the dislocation it cannot always be detected by roentgenograms at the end of six weeks when the patient is ready to resume walking. Ordinarily from three to four months are required for sufficient atrophy to occur before the contrast between living and dead bone is distinguishable in roentgenograms. Spontaneous reduction of a subluxation of the hip joint occasionally occurs immediately after the trauma so that the initial roentgenograms may appear entirely normal. However, if the displacement of the femur is of sufficient magnitude, aseptic necrosis of the head may result. When the patient is not forewarned of the possibility of late pain in the hip and continues to bear weight on the extremity after the return of symptoms, the head may undergo collapse with depression of the articular surface. These changes are at times irreparable and result from compression of dead trabeculae. Whenever possible, the extremity should be protected from weight bearing by means of crutches for four to six months after the postreduction period of immobilization. If roentgen evidence of aseptic necrosis of the head is not present at this time, the patient may resume full weight bearing with the likelihood that the head will remain alive, although roentgenographic follow-ups should continue for an additional twelve months. If, however, the head becomes necrotic early, protection can be provided and continued until serial roentgenograms show final revascularization and replacement by new bone. In young children aseptic necrosis following a dislocation of the hip appears somewhat similar to that observed in Legg-Perthes disease, and the immediate end results are equally satisfactory. When the femoral head in older children becomes necrotic, pathologic alterations simulate those seen in adults, and the results are equally poor. This appears to be true whether the primary pathologic condition was a traumatic dislocation, a fracture of the neck of the femur or a slipping of the upper femoral epiphysis.

*Arthroplasty of the Hip Joint.*—Albee and Preston<sup>574</sup> review some of the difficulties associated with arthroplasty of the hip with the use of the vitallium cup. They believe that vitallium cannot resist infection

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573. Banks, S. W.: *Aseptic Necrosis of Femoral Head Following Traumatic Dislocation of Hip: Report of Nine Cases*, J. Bone & Joint Surg. **23**:753-781 (Oct.) 1941.

574. Albee, F. H., and Preston, R. L.: *New Vitallium Cup for Arthroplasty of Hip*, J. Internat. Coll. Surgeons **4**:289-293 (Aug.) 1941.

as well as autogenous membranes, although it does possess such characteristics as indestructability, compatability with living tissues and resistance to body fluids. They feel that the design of the cups hitherto employed is faulty in that there is no inhibition of the proliferation of new bone or osteophytes about their margins. This may result in the recurrence of ankylosis or a bony blockage to free motion. The second criticism offered is that the cup by virtue of its rounded contour capsizes as soon as pressure is brought to bear on its edges, particularly if laxity of the abductor muscles is present. This laxity usually results from too short a kinesiological lever.

The cup described by the authors is so made as to conform to the rim of a normal acetabulum, and the flanges are adapted to fit completely over its rim. A bolt fixes the flanges to the region of the anteroinferior spine of the ilium, anchoring the cup so that there is no possibility of its being displaced or capsizing. These flanges also completely inhibit the possibility of a sleeve of bone forming about the acetabulum or the neck of the femur, and in this way reankylosis is prevented. Albee and Preston have also developed new reamers which may be inserted into the hip joint with the handle clamped on at any point around the periphery. This permits accurate shaping of the head and the acetabulum without the necessity of dislocating the hip.

The authors also feel that the results are poor in a large group of cases because of a shortening of the kinesiological lever. If this condition is present, it should be lengthened either at the time of the arthroplasty or at a later date.

Toumey<sup>575</sup> prefers the vitallium cup arthroplasty to other operative procedures and conservative treatment for *malum coxae senilis*. After the operation adhesive traction is applied, and gentle active and passive motion is begun almost immediately. Four weeks after the operation patients are allowed to walk with the aid of crutches and exercise on a stationary bicycle. If adduction contracture is present, tenotomy is performed either at the time of the major procedure or about one week later.

Since July 1939, 22 vitallium cup arthroplasties have been performed at the Lahey Clinic, Boston. The results were good in 16 cases and fair in 2. The condition was unchanged in 3 cases, and the result was poor in 1 case of rheumatoid arthritis with an ankylosed hip on the opposite side.

[ED. NOTE: We believe that correction of deformity, particularly of an adduction deformity, is of great importance as a preliminary step to arthroplasty of the hip joint.]

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575. Toumey, J. W.: *Surgery of Arthritis of Hip and Knee*, S. Clin. North America **21**:895-901 (June) 1941.

Cole<sup>576</sup> has had occasion to examine 2 femoral heads and microscopic sections from them after a vitallium cup arthroplasty. In the first case the patient had been walking for nearly six months, and replacement of a defective cup was necessary. In the second case no weight bearing and little motion had taken place on account of the condition of the patient, who died one month after operation. In neither of these did the author find the cartilage mentioned by Smith-Petersen, and it is probable that its development depends on longer use of the hip, as one of the latter's two specimens was twenty-one months post-operative and the other twenty-five months. In the first case on removal of the cup a beautifully shaped smooth bluish surface was exposed which appeared to be cartilaginous but which was covered by a thin membrane extending to it from the capsule. Similar findings were present on the surface of the acetabulum. A block of bone removed from the center of the head and examined microscopically showed no cartilage but merely a thin fibrous layer over compact bone. In the second case the cup was still loose, and the stump of the neck was rounded and smooth with irregular islands of what appeared to be cartilage scattered over its surface. Histologically, however, no cartilage was found, and the surface was covered with organizing fibrous tissue.

The postoperative treatment for this procedure is carefully outlined by the writer.

*Reconstructive Operations.*—Albee<sup>577</sup> reports that in partial paralysis of the muscles about the hip joint the kinesilogic lever, i. e. the lever formed by the head, the neck and the greater trochanter, is of great importance. It is identical in mechanical principle with that of the olecranon process. The pathologic condition, the weight-bearing stability and the function of the hip joint are markedly influenced by the balance between the length of this lever and the strength of the muscles pulling on it. In cases of infantile paralysis the lever is often not of normal physiologic length because of the weakening of the attached trochanteric muscles. To increase the power of flexion and abduction this lever should be lengthened laterally and anteriorly. In cases in which there is weakened extension and abduction, the lever should be lengthened laterally and posteriorly.

A strong shell of bone from the superolateral surface of the greater trochanter about  $4\frac{1}{2}$  inches (11.4 cm.) in length,  $1\frac{1}{2}$  inches (3.8 cm.) wide and  $\frac{5}{8}$  inch (1.6 cm.) thick with the muscular insertions undisturbed is turned outward and held in that position by a bone graft of adequate dimension. In addition to infantile paralysis, shortening of the neck of

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576. Cole, W. H.: Use of Vitallium in Surgery with Special Reference to Cup Arthroplasty, *Proc. Roy. Soc. Med.* **34**:779-782 (Oct.) 1941.

577. Albee, F. H.: Surgical Elongation of Kinesilogic Hip Lever in Partial Paralysis, *J. Internat. Coll. Surgeons* **3**:512-516 (Dec.) 1940.

the femur caused by destructive lesions or by arthroplasty may be an indication for this operation. In the author's experience excellent results have been obtained in such cases.

The operative technic is described in detail. After the operation immobilization is maintained in a double hip spica cast in moderate abduction for four weeks.

Milch<sup>578</sup> has again emphasized the causes of poor results of osteotomies of the Lorenz type. He finds that paradoxically the roentgenographically satisfactory bifurcations almost invariably result in marked disability of a definite type.

Pain was present in varying degree. In some cases the pain was so mild that it was overlooked in the satisfaction at the restoration of stability. In others it was so severe that the patients insisted on relief. There was always an annoying increase in the intercrural distance with an inability to bring the legs into parallel position. The patients could not completely flex or adduct the thighs. In the seated position they could not cross their legs tailor fashion. They could not assume the squatting position and had difficulty in putting on their shoes and stockings. In the erect position they stood with the legs abducted and the feet everted. Forward progress was possible only with a peculiar twisting and waddling gait, despite the fact that the Trendelenburg sign was usually absent.

On the other hand (and notably in children), it was observed that as the prong of the shaft fragment disappeared in the roentgenograms the pain and the disability vanished, usually without loss of the stability.

Such marked improvement, invariably observed in children following absorption of the bony prong, suggested that in adults in whom disability persisted similar relief might be obtained by surgical amputation of the offending spike of bone.

Milch has studied the action of the spike of bone on the skeleton. The external ischial border together with the posterior rim of the acetabulum forms a ridge which, except for the flare of the ilium, presents the most lateral projection of the pelvis. It is apparent, therefore, that when the osteotomized shaft makes contact with the pelvis at any point other than along this ridge the point of contact must lie medial to the ridge and must lead to interference with rotation when the femoral head is fixed.

The head of the femur was dislocated posteriorly onto the ileum, and the experiments were repeated. Essentially with one exception the same results were obtained. When the osteotomized shaft was displaced into the acetabulum according to the described technic of the

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578. Milch, H.: "Pelvic Support" Osteotomy, *J. Bone & Joint Surg.* **23**:581-595 (July) 1941.

operations, the most marked limitation in all arcs of motion was obtained. This was immediately recognized as being caused by the steeply sloping walls of the acetabular cavity, which, like the ridge, acted to obstruct the motion of the spike. This observation is of especial significance, because of the expressed opinion that "the osteotomy is merely the preparatory step in the bifurcation operation. The essential act is the reposition of the distal fragment into the acetabulum." On the contrary, it was found that in the presence of a femoral head and neck the acetabular position of the distal fragment was the worst of all the sites of pelvic abutment and that the consequent limitation of motion could be overcome only by resection of the spike. However, when the femoral head and neck were amputated, the acetabular position of the fragment acted to restore good balance and stability without limitation of motion. Though this outcome could have been predicted from the principle that simultaneous universal motion about each of two separate point fulcrums is impossible in three dimensional space, the studies have demonstrated conclusively that the acetabular position of the bifurcation spike is to be avoided except in treating those conditions in which the instability results from a pathologic loss of the head and the neck.

In accordance with these findings the author has found that resection of the projecting spike of the shaft fragment eliminates the second point of pelvic abutment, that motion is restored and that the pain is relieved without loss of stability.

The author has noted also that excessive pelvic tilt is present in unilateral cases when excessive abduction of the distal fragment is found. In his opinion this could be overcome by making sure that the angle between the shaft and a line connecting the femoral head to the upper end of the distal fragment was not more than the angle of normal inclination of the outer wall of the level pelvis.

The therapeutic implications of these considerations are obvious. Care should be taken to avoid the production of a projecting spike at the site of osteotomy or resection of this prominence should be done if it has formed. The osteotomy should be carefully planned in order to avoid a postosteotomy angle which is in excess of the angle of normal pelvic inclination (210 to 230 degrees). The author feels that a revision of old osteotomies is indicated if either of these factors is found to be interfering with good function.

[ED NOTE: This article is of a highly technical character, and we suggest that it be read in detail by those who are interested in the bifurcation operation.]

*Subtrochanteric Osteotomy.*—Franck and Kiaer<sup>579</sup> report on the reexamination of 43 patients with old congenital dislocation of the hips

579. Franck, S., and Kiaer, S.: Palliative Subtrochanteric Osteotomy, *Acta orthop. Scandinav.* 11:153-171, 1940.



who were treated by palliative subtrochanteric osteotomy during the period 1926 to 1935. In the authors' opinion the indications for this operation are subjective and objective symptoms. The subjective symptoms are pain and fatigue in and around the hip joint and in the lumbar region, the pain being aggravated by lifting. The objective signs are those resulting from impairment of the stability of the hip joint, such as waddling gait, the Duchenne-Trendelenburg symptom and increased lordosis.

Prior to operation 37 patients had both subjective and objective symptoms. Two patients were operated on because of subjective symptoms alone. Four patients had only objective findings. In all of the cases complete congenital dislocation of the hip was presented, and in 5 cases there was neoarthrosis. A total of 43 patients were treated with fifty-three osteotomies, a bilateral operation being performed in 10 cases. In the total estimation of the therapeutic results there were 27 bifurcation osteotomies of the Lorenz-Bayer type. Twenty-three were supporting osteotomies of the Drehmann type. Three Schanz osteotomies were performed, but these cases were not included in the evaluation of end results. In both the bifurcation and the supporting type of osteotomy the operation was done at the level of the acetabulum so that the osteotomy angle fell outside the socket. In all cases in which there was lordosis, an attempt was made to turn the osteotomy in the sagittal plane with the angle opening posteriorly. In evaluating the end results shortening was left out of consideration because the result was estimated after counterbalancing with corrective footwear. The average shortening resulting from the operation was about 2 cm. Of 21 patients treated with bifurcation osteotomy, 10 had excellent results; 6 had good results; 1 had a fairly good result, and 4 patients were unchanged. Of the 20 patients who were treated with the supporting osteotomy of Drehmann, 9 had excellent results; 4 had good results; 3 had fairly good results, and 4 were unchanged. The only difference noted between the results of the supporting and the bifurcation osteotomy was that after the bifurcation osteotomy the mobility of the hip joint was more impaired than after the supporting osteotomy although not to such an extent as to shift the clinical judgment of the results.

The authors have also attempted to correlate the end results with regard to the angle obtained by the osteotomy both in the frontal and in the sagittal plane. In regard to the osteotomy angle in the frontal plane two factors are of significance in relation to the stability of the hip: the placing of the axis of the lower extremity as near as possible to the midline and the tension of the gluteal muscles. Both of these requirements are met through the valgus position of the osteotomy. Franck and Kiaer point out that in children under the age of 16, the

osteotomy angle in the frontal plane should be one of marked valgus, about 130 degrees, to allow for self straightening of the osteotomy angle as growth progresses. They find that in the great majority of cases the Trendelenburg phenomenon is abolished or greatly improved when the frontal angle of the osteotomy is between 140 and 160 degrees. They note with particular interest that in 3 cases the Trendelenburg phenomenon was abolished even though the frontal angle was lacking. This occurred presumably because a good angle was present in the sagittal plane, thus pulling the trochanter sufficiently downward so that the tension of the gluteus medius muscle was improved. Of 7 patients on whom unilateral osteotomy was performed with a sagittal angle of 170 to 140 degrees, 6 showed improvement in their lordosis. In the seventh, however, lordosis was unchanged. In 11 cases in which there was no angle in the sagittal plane, the lordosis remained unchanged. In 6 cases of bilateral osteotomy with a sagittal angle of 170 degrees, there was severe lordosis present prior to the operation. On reexamination of the patients only slight or normal lordosis was demonstrated. In 7 cases with a good osteotomy angle in the frontal plane but with no osteotomy angle in the sagittal plane, there was no change in the lordosis. The authors feel that these findings justify the claim that the osteotomy angle in the sagittal plane is of significance to the correction of the lordosis.

The writers believe that the success of the operation depends on the adducted position of the proximal fragment above the osteotomy and on the downward turning of the trochanter, whether it be in the frontal, the sagittal or the intermediate plane, since this is the important factor in activating the gluteal musculature. The authors lay particular stress on the angle in the sagittal plane or the intermediate plane. They feel that an expedient angle in this direction is sufficient to activate the musculature of the buttocks and at the same time change the static conditions so that the lordosis is straightened out. If the upper displacement of the trochanter is so great that it does not seem likely that turning down of the trochanter will be sufficient to activate the gluteal musculature, this might be accomplished by moving the trochanter out after the method of Lexer or Albee.

*Miscellaneous.*—Plantenga<sup>580</sup> discusses the differential diagnosis of disease of the hip joint, especially in children, describing several cases of coxitis fugax which he defines as a nonspecific inflammation of the synovial membrane of obscure causation. This diagnosis may be arrived at only after ruling out such conditions as tuberculosis, osteomyelitis, and Legg-Perthes disease. Clinically, a history of heavy strain or exercise is found. The patient tends to keep the hip and the knee flexed and in slight external rotation. Swelling and pain on pressure over the hip

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580. Plantenga, B. P. B.: Coxitis Fugax, *Geneesk. gids* 19:296-302 (April 18) 1941.

joint are present. Roentgen findings are normal. The cause may be toxic, traumatic or infectious-allergic. Some patients are cured after a few days' rest in bed. In others the condition may persist for a longer time and may require traction. The condition is more common than is supposed and is of importance because it has a good prognosis and should be differentiated from more serious conditions.

Delitala<sup>581</sup> presents a roentgen cinematographic study of the hip joint. In a patient with ankylosis of the hip motion takes place in a frontal plane through the lumbosacral articulation and through the normal joint. This combined motion in walking amounts to about 25 degrees, which is approximately the same as that occurring in a normal hip joint. The Roser-Nélaton line may be used as a standard to judge flexion angulation in patients with ankylosis. A favorable position would be an angle of 50 degrees to this line. A greater angle is good for standing but not for walking. Ankylosis in adduction, abduction, internal or external rotation is unfavorable and should be corrected.

Schein and Lehmann<sup>582</sup> review the literature regarding acute trochanteric bursitis with calcification and report on the findings in 7 cases. Four patients had complained of pain in the region previous to their illness on admission. Two had calcific subacromial bursitis before or after the trochanteric involvement. The presenting symptoms were remarkably constant, i. e. severe pain in the hip region with inability to walk and with an onset usually less than forty-eight hours before examination. The outstanding physical findings were exquisite localized tenderness over the greater trochanter, severe on abduction and rotation of the hip with little or no pain on flexion and no tenderness over the hip joint proper. Roentgen examination showed calcification in all cases, but the density, the configuration and the position of the shadows varied. The total course of disability was about three days. The treatment consisted of rest in bed, the application of cold or hot compresses or local infiltration with procaine hydrochloride. In 4 cases in which the follow-up was from nine months to one year, there was no recurrence. Disappearance of the calcification was demonstrated by roentgenograms in 2 cases after one month. The pathogenesis of this lesion is similar to that of calcified bursitis about the shoulder. Clinical healing of the condition is associated with hyperemia, the increased vascularity causing absorption of the calcified deposit.

Francon<sup>583</sup> reports a single case of ischial bursitis with pain on coughing, sitting or walking over long distances. The pain was increased

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581. Delitala, F.: Deambulation in Ankylosis: Contribution to Articular Physiopathology, *Chir. d. org. di movimento* **26**:5-13 (July) 1940.

582. Schein, A. J., and Lehmann, O.: Acute Trochanteric Bursitis with Calcification, *Surgery* **9**:771-779 (May) 1941.

583. Francon, F.: Local Use of Procaine and Procaine Compounds in Therapy of Ischiatic Bursitis, *J. de méd. de Lyon* **22**:15-16 (Jan. 5) 1941.

by slight adduction and internal rotation of the thigh. Repeated injections of procaine hydrochloride into the tender area over the ischial tuberosity gave complete relief of symptoms.

Blixenkrone-Møller<sup>584</sup> has used extrapelvic resection of the obturator nerve in several cases of osteoarthritis of the hip joint. Of 6 patients with adduction contractures, 5 showed improvement while 1 was unimproved. In 3 cases without adduction contractures there was no improvement. There seemed to be no relation between the degree of arthritis and the relief obtained from this procedure. The author feels that Camitz is correct in his view that the pain in disease of the hip is due to spasticity of the adductor muscles, but only in those cases presenting an adduction contracture.

In 7 cases of secondary arthritis deformans only 1 patient secured relief from pain; this was the patient with bilateral dislocation of the hip. In certain cases resection of the obturator nerve is not adequate to relieve pain. Roentgen therapy should be kept in mind as it may render some of these patients free from pain.

#### XV. CONDITIONS INVOLVING THE KNEE JOINT

*Function and Mechanics.*—Brantigan and Voshell,<sup>585</sup> after a study of approximately 100 knee joints, many of which were in the fresh condition, have clarified many questions as to the functions of the ligaments and the menisci of the knee joint. They have found that lateral and rotary motions of the knee joint in extension are controlled by the capsule, the collateral ligaments and the cruciate ligaments and that in flexion they are controlled by the same structures except for the fibular collateral ligament.

Forward gliding of the tibia on the femur is controlled by the anterior cruciate ligament, whereas backward gliding is controlled by the posterior cruciate ligament. Lateral gliding of the tibia on the femur is controlled by the tibial intercondyloid eminence and the femoral condyles with the aid of all the ligaments. Hyperextension is controlled by both collateral ligaments, both cruciate ligaments, both menisci, the posterior aspect of the articular capsule, the oblique popliteal ligament and the structure of the femoral condyles.

Hyperflexion is controlled by both cruciate ligaments, both menisci, the femoral attachment of the posterior aspect of the capsule, the femoral attachment of both heads of the gastrocnemius muscle and the osseous structure of the condyles of the femur and the tibia.

584. Blixenkrone-Møller, N.: Treatment of Arthritis Deformans of the Hip by Resection of the Obturator Nerve, *Acta orthop. Scandinav.* **11**:11-30, 1940.

585. Brantigan, O. C., and Voshell, A. F.: Mechanics of Ligaments and Menisci of the Knee Joint, *J. Bone & Joint Surg.* **23**:44-66 (Jan.) 1941.

The menisci cushion hyperextension and hyperflexion. Although the medial meniscus and the tibial collateral ligament are closely related, there is no strong fibrous tissue attachment between them. Also, this ligament glides forward and backward in extension and flexion, and some portion of it is always taut. The capsule of the joint is in the most relaxed position when 15 to 30 degrees of flexion is obtained. The medial femoral condyle acts more nearly as the axis of rotation of the knee joint.

If the anterior cruciate ligament and the tibial collateral ligament are ruptured, both probably should be repaired, although repair of either alone usually gives a satisfactory functioning knee joint.

[ED. NOTE: This article represents an important contribution to orthopedic surgery.]

*Function and Structure.*—Kostler<sup>586</sup> is of the opinion that the joint fluid and lymph are not sufficient to nourish the menisci. The blood supply plays an important part. The results of his experiments with animals support the work of Gebhardt, in that Kostler found that bionecrosis may take place if the blood supply to the menisci is damaged. He concludes that damaged softened menisci should be left in the knee only if they contain living healthy blood vessels. [ED. NOTE: The importance of degenerative changes in semilunar cartilages has been underemphasized.]

*Wounds and Injuries.*—Speaking from experience gained in the first World War and in the evacuation of Dunkirk, Ogilvie<sup>587</sup> writes that immobilization of any injury of the knee from the earliest moment until infection has been averted or overcome is the key to success. The value of the treatment of injuries of the knee with sulfanilamide is acknowledged.

Most wounds seen within six hours should be debrided, packed with sulfanilamide (dry or mixed with petrolatum) and then immobilized in a plaster spica cast. The synovial cavity may be closed with the finest of catgut but not the capsule. The sutures in the skin should be placed loosely. If evacuation of the patient becomes imperative, the surface sutures should always be removed first, regardless of the condition of the wound. If serious damage to the blood vessels and the nerves is present, amputation should not be delayed.

If the wound is seen within six to twenty-four hours after infliction, some of it still can be debrided. Immobilization and sulfanilamide therapy usually are continued, and the wound should be watched care-

586. Kostler, J.: Trophic Disorders of Meniscus: Experimental Study, *Arch. f. klin. Chir.* **199**:49-61, 1940.

587. Ogilvie, W. H.: Wounds of Knee Joint, *Lancet* **1**:471-473 (April 12) 1941.

fully for signs of sepsis. The battle for a septic knee is usually decided within four days. If sepsis is present, the knee should be drained, and immobilization should be continued. If the patient is not better at the end of four days, it is usually better to amputate.

Palmer<sup>588</sup> briefly discusses injuries of the knee joint sustained in football. These may cause acute or chronic inflammation of any of the thirteen bursas about the knee, but those most commonly affected are the ones on the front and the outer side. Infection of these bursas may result from penetrating wounds and metastatic infections. Other common conditions resulting from trauma are: (1) acute synovitis due usually to injury over the internal femoral condyle; (2) tearing of the capsule with or without rupture of the internal lateral ligament; (3) injury to the internal semilunar cartilage, and (4) Baker's cysts. Palmer states that the injection of 2 to 5 drops of tincture of iodine when the internal semilunar cartilage is loose only in the central portion often will produce enough adhesions to fix the cartilage firmly to the capsule.

Leger and Delinotte<sup>589</sup> advocate early repair of tears of the lateral ligaments. They report 4 cases of severe strain of the knee with tear of the internal ligament and 1 of tear of the external lateral ligament. The 5 patients were operated on within a week to a month after injury. In 2 cases of repair of the internal lateral ligament, the ligament was reinforced by plication of the capsule. In 1 case of tear of the external lateral ligament, the ligament was reinforced with the biceps femoris tendon. It was too soon at the time the authors wrote for final analysis of the results, but they apparently will be better than would have been achieved by conservative means.

LeRoy,<sup>590</sup> in reporting cases of recent traumatic hemarthrosis, advocates aspiration of blood from the knee and injection of 10 cc. of a 1 per cent solution of procaine hydrochloride. [ED. NOTE: These radical views on the treatment of acute ligamentous tears about the knee are perhaps worthy of notice.] He reports 9 cases in which this treatment was used: Satisfactory results were achieved in 7 cases after one injection and in 2 cases after two injections.

*Wounds and Injuries of the Knees.*—Evans,<sup>591</sup> who has had extensive experience with injuries of the knee among athletes at the University of

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588. Palmer, D. H.: Football Injuries to Knee Joint, *Northwest med.* **40**: 143-145 (April) 1941.

589. Leger and Delinotte: Grave Sprain of the Knee: Four Cases, *Mém. Acad. de chir.* **66**:861-868 (Nov. 27-Dec. 11) 1940.

590. LeRoy, A.: Therapy of Recent Traumatic Hemarthrosis of the Knee, *Mém. Acad. de chir.* **66**:648-652 (Oct. 16-30) 1940.

591. Evans, E. T.: Internal Derangement of the Knee in the Athlete, *Bull. Minnesota M. Found.* **3**:11 (Nov.) 1941.

Minnesota, classifies such injuries as: (1) simple sprains with effusion; (2) torn lateral ligaments; (3) torn crucial ligaments; (4) torn semilunar cartilages, and (5) recurrent disability from old injury. His treatment of torn semilunar cartilages consists of the application of cold packs, aspiration, traction (rather than manipulation) to unlock and then operation.

The treatment of war wounds of the knee has been reviewed by Fisher.<sup>592</sup> He emphasizes the seriousness of wounds of joints and the need for prompt care of them. The following principles of treatment are laid down: 1. Treat promptly. 2. Treat shock. 3. Make roentgenograms. 4. Use aseptic technic. 5. Give sulfanilamide orally and locally.

A suitable knee brace has always been hard to find. Jordan<sup>593</sup> introduces one made of woven elastic, reinforced in front with leather straps and containing a vertical piece of spring steel posteriorly which has a piano hinge at the popliteal fossa. It is stated that this brace allows flexion but at the same time increases lateral stability.

An interesting case of irreducible lateral dislocation of the patella with rotation, so that the articular surface was turned away from the femoral condyle, is reported by Inman and Smart.<sup>594</sup> Open reduction was necessary; at the same time the torn tendons also were repaired.

*Rupture of the Tendon of the Quadriceps Femoris Muscle.*—Martin<sup>595</sup> emphasizes that the treatment of rupture of the tendon of the quadriceps femoris muscle is surgical unless the rupture is unmistakably incomplete and exhibits signs of prompt healing. Stainless steel wire usually is preferred as the means by which the tendon is approximated to the patella.

In old injuries the scar tissue is not resected but is divided and dissected upward to the tendon so that the scar tissue forms a strap or apron with which to pull down the retracted tendon. After the tendon has been sutured to the patella, this apron of scar tissue is sutured over the anterior aspect of the patella. Sometimes, if the sutures of silk or wire are under undue tension, they can be reinforced with fascial bands. After surgical repair, functional stimulation by means of guarded use of the joint should be permitted as early as safety permits to combat muscular atrophy.

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592. Fisher, A. G. T.: Treatment of War Wounds of Knee Joint, M. Press **205**:454-457 (June 4) 1941.

593. Jordan, H. H.: New Elastic Knee Brace with Posterior Hinge, M. Rec. **153**:87-88 (Feb. 5) 1941.

594. Inman, V. T., and Smart, B. W.: Irreducible Lateral Dislocation of Patella with Rotation: Case, J. Bone & Surg. **23**:695-700 (July) 1941.

595. Martin, J. W.: Rupture of Quadriceps Femoris Tendon, Nebraska M. J. **26**:11-12 (Jan.) 1941.

*Arthrodesis.*—Hellstadius <sup>596</sup> points out that acceleration of the consolidation and consequent shortening of the immobilization time can be obtained by compression of the resected ends of bone against each other. This also lowers the risk of formation of pseudarthrosis. The author describes a quadrangular metal frame one side of which is movable with a vertical supporter in each of the four corners. These supporters can be fastened to Kirschner wires which have been passed through the bone ends above and below the resected knee joint. By means of a screw the movable side of the frame with its vertical supporters can be approximated to the opposite side, and through the resulting pull on the Kirschner wires the resectional surfaces can be brought into close approximation and even compression. The apparatus is recommended especially for use at the ankle and also at the astragalo-calcaneal joint, but in these instances the proximal pair of supporters take hold of the Kirschner wire at the upper end of the tibia, while the other pair of supporters are fastened into heavy loops of cord which are incorporated in the plaster of the leg. The usual type of plaster of paris cast is always applied, but windows are cut in the plaster around the Kirschner wires when arthrodesis of the knee is to be done, while the cast does not extend to the Kirschner wire when arthrodesis of the joints below the knee is to be done. [ED. NOTE: Such a piece of apparatus deserves more widespread trial.]

*Dercum's Disease.*—McGavack and Klotz <sup>597</sup> report a case of juxta-articular adiposis dolorosa (Dercum's disease) in which there were unusual neurologic phenomena. Impairment of joint function was omnipresent in this case, as well as in more than 500 cases reported. Inability to control the legs or to bear weight on them is far from rare. The authors state that it is logical to accept adiposity, asthenia, pain, psychic disturbances and neurologic manifestations as the outstanding phenomena in Dercum's disease, that each may be present in varying degree and that superimposed on them may be secondary conditions, such as hypochromic anemia, certain types of arthropathy and the like.

In the case presented symptoms were confined mainly to the lower extremities. Roentgenograms of the patient, a 63 year old white woman, disclosed osteoarthritis of the knee joints, muscular atrophy and an increase in subcutaneous tissue throughout the lower extremity.

596. Hellstadius, A.: Apparatus for Firm Apposition of Resectional Surfaces of the Knee in Intra-Articular Arthrodesis, *Acta orthop. Scandinav.* **11**:190-198, 1940.

597. McGavack, T. H., and Klotz, S.: Juxta-Articular Dercum's Disease: Case Report, *New York M. Coll. & Flower Hosp. Bull.* **3**:299-305 (Dec.) 1940.



*Baker's Cyst.*—In a reprint of Baker's <sup>598</sup> second communication concerning the formation of synovial cysts first published in 1885 it is concluded that abnormal synovial cysts may be formed in communication not only with the knee but also with the shoulder, the elbow, the wrist, the hip and the ankle joints. He warns that direct communication between the joint and the abnormal synovial cyst frequently is deceptive and should not lead to the inference that no such communication exists. [ED. NOTE: The conditions which are now classified as synovial cysts arising from joints, ganglions and bursas are not distinguished separately by Baker, and he apparently is of the opinion that all arise from distention of the synovia of the joint. In some of the cases reported in which the condition has arisen in locations other than the knee, it seems in accord with present knowledge to represent bursal inflammation, and 1 patient referred to by Baker but observed by another author probably had tuberculous tenosynovitis.] Baker states his suspicion that in some cases a relation to osteoarthritis existed and that in others there was a relation to the condition which would now be called tabetic arthropathy or Charcot's joint.

*Osgood-Schlatter Disease.*—Jentzer and Perrot <sup>599</sup> discuss the causation of Osgood-Schlatter disease and present the results of pathologic studies made in 4 cases. Definite conclusions could not be drawn, but they believe that a predisposing factor is present in all cases. They advocate excision of the tubercle and believe the period of disability is shortened by this procedure.

*Synovectomy.*—Ghormley and Cameron <sup>600</sup> report on 103 knee joints operated on at the Mayo Clinic, Rochester, Minn., in which synovectomy was performed. They state that the best indications for the operation are: (1) traumatic arthritis; (2) synovial osteochondromatosis, and (3) xanthoma or benign tumors. The next best indications for synovectomy are: (1) chronic infectious arthritis; (2) chronic synovitis, and (3) intermittent hydrarthrosis. These indications are much in accord with those for synovectomy reported by Magnusson.<sup>601</sup> He states that the best indication is nonspecific inflammation of the synovia; this probably is the classification group in which traumatic arthritis, as listed just previously, would be placed. He reports the performance of synovectomy ten times for 9 patients with good results.

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598. Baker, W. M.: Baker's Cyst: Formation of Abnormal Synovial Cysts in Connection with Joints, *M. Classics* 5:805-820 (May) 1941.

599. Jentzer, A., and Perrot, A.: Osgood-Schlatter's Disease, *Helvet. med. acta* 8:162-174 (April) 1941.

600. Ghormley, R. K., and Cameron, D. M.: End-Results of Synovectomy of Knee Joint, *Am. J. Surg.* 53:455-459 (Sept.) 1941.

601. Magnusson, R.: Total Synovectomy of Knee Joint, *Acta orthop. Scandinav.* 11:235-263, 1940.

*Meniscuses.*—In a ten-year review of internal derangements of the knee, Cave and Staples<sup>602</sup> have found that congenital anomaly of the meniscuses occurred in 2.4 per cent of the cases. They review the symptoms and signs and emphasize the point that the lateral meniscus normally is the one involved. Treatment is by surgical excision, whether the meniscus is damaged or not.

Gallagher<sup>603</sup> reviews the method he employs in the preoperative and postoperative care of fractured semilunar cartilages. He stresses two points: first, that only half of the cartilage should be removed at a time; and second, that routine dressings should be applied twenty-four and forty-eight hours postoperatively with aspiration of the contents of the joint if any excess fluid is present. The average time before his patients are allowed to return to work is seven weeks.

*Osteochondromatosis.*—Wilmoth<sup>604</sup> reports the results of a follow-up study made in 10 cases of osteochondromatosis involving the knee, the elbow or the hip joint. In none of the cases in which surgical removal of the loose bodies was carried out was there any tendency toward the formation of new loose bodies. The longest period for which any of the patients were followed after operation was four years. In the knee joint the loose bodies occurred fairly constantly in the posterior compartment. If the loose bodies were confined to this space, the synovial membrane there was thickened, but the rest of the synovial membrane was normal. When the bodies occurred throughout the joint, all the synovial membrane was thickened. The symptoms noted were those of arthritis rather than any sudden pain, and when loose bodies were present, excision of them always was advised. Synovectomy was done when the synovial membrane was found to be thickened.

(To Be Concluded)

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602. Cave, E. F., and Staples, O. S.: Congenital Discoid Meniscus: Cause of Internal Derangement of Knee, *Am. J. Surg.* **54**:371-376 (Nov.) 1941.

603. Gallagher, C. A.: Our Method of Care of Fractured Knee Cartilages, *J. Oklahoma M. A.* **34**:237-239 (June) 1941.

604. Wilmoth, C. L.: Osteochondromatosis, *J. Bone & Joint Surg.* **23**:367-374 (April) 1941.

## REVIEW OF UROLOGIC SURGERY

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### KIDNEY

*Crush Syndrome and the Kidney.*—A number of timely and exceptionally important articles dealing with the effect on the kidney of trauma to other parts of the body have recently appeared.

Bywaters<sup>1</sup> states that in a typical case in which the patient is severely injured and has a history of, for instance, being buried for several hours with masonry resting across a limb, such a patient will be shocked on admission or soon after, with a decrease in blood pressure which follows a preliminary period of apparent well-being. During this initial phase hemoconcentration occurs (and compensatory vasoconstriction) because of loss of plasma into the injured part, which becomes swollen and hard. There is also loss of sensation and power; the skin shows whealing and, later, blisters. Arterial pulsation distally may be impaired. After restoration of blood volume by the transfusion of blood or serum the patient recovers, but it is noticed that the urine is blood stained and contains albumin and pigmented granular casts. During the next few days the urinary output decreases and the urine becomes

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1. Bywaters, E. G. L., in Discussion on the Effects on the Kidney of Trauma to Parts Other Than the Urinary Tract, Including Crush Syndrome, Proc. Roy Soc. Med. **35**:321-328 (March) 1942.

clearer; the blood pressure increases to a high value; there is a progressive increase in blood urea, phosphate and potassium and a decrease in alkali reserve. The patient becomes alternately drowsy and apprehensive; death occurs suddenly on about the seventh day and is occasionally preceded by abnormalities of cardiac action similar to those produced experimentally by intoxication with potassium.

If death does not occur before the usual time from some other cause, the kidneys are swollen and wet. The most obvious feature microscopically is the presence of pigment casts in the collecting tubules similar to those seen in the urine. More important, Bywaters believes, are the severe tubular damage seen in the distal convoluted tubules and Henle's loop of the boundary zone—often with complete necrosis—and the discharge of hyaline casts into the interstitial tissue and surrounding cellular reaction. This corresponds to the biochemical indication of tubular dysfunction and leakage.

The critical period is reached toward the end of the first week; most patients who survive to the eighth or ninth day will recover. The surviving patients (who amount to about a third of the patients in the total number of collected cases) have been in general less severely injured than those who died. The severity of the injury must be judged by the amount of tissue rendered necrotic, hence (when the circulation has been reestablished) by the amount of hemoconcentration produced by loss of plasma into the damaged zone. The severity of the renal lesion must be judged by the increase in blood urea and blood pressure, by the urinary output and by tubular function as measured by the percentile concentration of urinary urea as compared with that in the blood. A good prognosis may be given for the patient who has inextensive injuries, and a relatively good one is associated with injuries so severe that there is no reestablishment of the circulation to the part. A good prognosis may be given if the patient has a decreasing value for blood urea or, since there is a progressive increase in most cases in which the outcome is fatal, a value for blood urea less than the value that would be expected for the time after injury. In cases in which injury is fatal, the curve for the concentration of blood urea rises steadily until death supervenes on or about the seventh day. Concentration among surviving patients may describe such a curve and then decrease, or it may fail to increase as much and may decrease earlier. The decrease is associated with diuresis. At the same time hypertension disappears. Persons rescued from collapsed houses usually have been treated first for shock; then the circulation to the injured limb has been reestablished, and the kidneys have not been considered until the fourth day after injury; but if instead of this procedure such patients had been treated first of all for renal failure and then given the benefit of establishment of good alkaline

diuresis as soon and as rapidly as possible, followed by, finally, treatment of shock and local lesion, the mortality rates would have been lowered, Bywaters believes.

Belsey<sup>2</sup> discusses the effects on the kidney of trauma to parts other than the urinary tract, and he includes the crush syndrome in his remarks.

In the crushed limb the following changes have been observed: First, necrosis of muscle, patchy in distribution and rarely corresponding to portions of damaged overlying skin, such as would suggest that the necrosis is caused by direct pressure. The muscle is pale and mottled. Hemorrhage into the muscle or the tissue planes is not constant. There are edema of the limb and an increase of tension in the tissues within the fascial compartments of the limb. During life evidence of impairment of peripheral circulation and sometimes of absence of pulsation is found, but at necropsy there is rarely evidence of thrombosis or gross damage to the main arteries of the limb, although in a few instances rupture of a major vessel has been found.

Loss of neural function has been recorded in the majority of cases and has commonly involved all the nerves of the limb, a distribution suggesting that the failure of conduction is caused by ischemia and asphyxia rather than by direct pressure. Among patients who have survived, the recovery of neural function has been steadily progressive for six to twelve weeks and usually has been complete.

In the future, Belsey states, there must be more control of and attention to the time factor. It is now known that spontaneous recovery can occur, and difficulty arises from the fact that treatment to be of any avail probably will have to be started early, before it becomes obvious on the basis of the rapidly diminishing output of urine that the patient is a member of that group in which death inevitably occurs between the sixth and the ninth day with complete anuria.

Little in the way of operative treatment has been employed as yet, and probably rightly. Belsey says that primary amputation has been performed in 3 cases, in 2 of which death occurred. In the first case, in which the patient was a girl 17 years old whose left leg had been crushed for nine hours, amputation was performed through the thigh and apparently above the level of tissue damage. This was carried out at the thirty-sixth hour after the injury, because of incipient gangrene of the limb. There was no evidence of damage to other limbs. Death occurred on the sixth day, in the presence of almost complete suppression of urine.

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2. Belsey, R., in Discussion on the Effects on the Kidney of Trauma to Parts Other Than the Urinary Tract, Including Crush Syndrome, *Proc. Roy. Soc. Med.* 35:328-332 (March) 1942.

Decompression of the limb by incision into the deep fascia has been done in 7 cases, of which only 3 have been recorded so far. Three patients died and 4 survived.

Decapsulation of the kidneys was performed in 1 case in which renal failure was established, but the patient died.

In none of the published reports of cases is there evidence that operative surgical treatment played any part in saving the life of the patient. The case for amputation remains unproved. Ablation of crushed arms probably is never indicated; but in view of the poor prognosis which accompanies extensive crushing of the leg, the application of a tourniquet to the limb before or at the time of release from the crushing force by a competent physician attached to the rescue squad followed by early amputation as soon as shock has been controlled appears to be rational. Yet Belsey admits that many limbs might be sacrificed unnecessarily by such a course and says that until the crush syndrome can be reproduced experimentally and the fatal renal complications averted by early amputation, such reasoning should be applied to treatment of human beings only with extreme caution.

McMichael<sup>3</sup> discusses the effects on the kidney of trauma to parts other than the urinary tract, and he includes the crush syndrome in his consideration. He states that although final conclusions regarding therapy cannot be arrived at the problem of treatment can now be approached on a rational basis. Instead of the physician's waiting two or three days to find out whether or not renal damage is manifest, he must consider the state of the kidney from the outset. It should be impressed on members of rescue parties that the real danger threatening people who have crushed limbs is that of renal failure. Before the patient is released, therefore, every effort should be made by means of the abundant employment of warm drinks to insure a good flow of urine. The advantage of good diuresis may be: (1) dilution of chemical poisons within the renal tubules and (2) prevention of precipitation of myohemoglobin casts.

Alkalinization of the urine seems to be advantageous, and it is certainly a rational procedure to give alkalis, because the alkaline reserve of these patients often is greatly reduced. Sodium bicarbonate and sodium citrate should be administered orally from an early stage twice to three times an hour, in doses of 2 to 4 Gm. Other diuretic agents can be tried, but there is little evidence as yet to favor any particular one. Administration of a 10 per cent solution of the sodium salt of ortho-hydroxy-mercuric-methoxy-propylcarbamylyphenoxy-acetic acid (mer-

3. McMichael, J., in Discussion on the Effects on the Kidney of Trauma to Parts Other Than the Urinary Tract, Including Crush Syndrome, *Proc. Roy. Soc. Med.* **35**:333 (March) 1942.

saly) has been a failure more often than it has succeeded, and since this drug may be a tubular cell poison, it is safer to avoid its use.

Riddell <sup>4</sup> discusses the effects on the kidney of trauma to parts other than the urinary tract, and he mentions the crush syndrome. He says that if a large number of casualties are admitted to the hospital, it is easy for physicians to miss the early crush syndrome unless the casualties are systematically examined. Such a patient often seems to be in good condition and for this reason may temporarily be passed over, so to speak, in favor of examination of some one in a neighboring bed who appears to be more dangerously ill. The only way to avoid this and other mistakes, Riddell says, is to examine each patient in turn, however rapidly, from head to foot, and then if the crush syndrome does not chance to be present, the telltale wheals or simply a localized erythema of the skin will draw attention to the lesion. The nurse in charge can then be warned as to what is likely to happen; the first quantity of urine passed can be saved, and investigation can be begun at the earliest moment.

Robertson and Mathews <sup>5</sup> discuss the crush syndrome and report a case. They say that the duration of the crushing varies greatly and that there does not appear to be any direct relation between the duration and the subsequent seriousness of the condition. The shortest period recorded of crushing which has been followed by the development of the crush syndrome is three hours, and the longest, twenty-six hours. The average period is about ten hours.

In addition to the evidences of shock, physical examination at the outset discloses tenderness and edema and sometimes bruising over the affected parts. There may be whealing of the skin; if this is not present early, it frequently develops later. The involved limbs often are partially or completely paralyzed, and sensation usually is diminished or absent. Arterial pulsation may be reduced, and in several cases in which the edema has progressed, pulsation has disappeared entirely.

Initial shock apparently is controlled by ordinary measures, such as rest in bed, the application of heat and the administration of morphine sulfate. Later, shock reappears and is evidenced by pallor or cyanosis, cold sweating of the extremities, rapid pulse, subnormal temperature, low blood pressure, leukocytosis and, in almost every case, marked hemoconcentration. This episode is controlled by more vigorous measures, such as the administration of oxygen and the intravenous administration of fluids.

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4. Riddell, V. H., in *Discussion on the Effects on the Kidney of Trauma to Parts Other Than the Urinary Tract, Including Crush Syndrome*, Proc. Roy. Soc. Med. **35**:334 (March) 1942.

5. Robertson, H. R., and Mathews, W. H.: *Crush Syndrome*, Canad. M. A. J. **46**:116-120 (Feb.) 1942.

During the course of the next few days shock does not recur but the patient remains ill. He is drowsy and apprehensive and vomits frequently. The tongue is dry and coated and the breath foul. The blood pressure tends to increase daily. The urinary output is low, and the values for blood urea and blood potassium are high. Edema increases, and, particularly if the administration of fluid is forced, the blood becomes more and more dilute.

Recovery is heralded by an increase in urinary output with a corresponding decrease in the edema and lowering of the values for urea and potassium in the blood. Blood pressure declines as recovery progresses. As a rule, if the patient survives the affected limb returns to normal.

Death, when it occurs, comes rather suddenly—somewhere between the seventh and the tenth day. The mortality rate associated with the condition is difficult to assess at present. Undoubtedly many patients whose condition may be mild or severe escape notice. Study of the reported cases reveals that few patients in whom the syndrome was fully developed survived.

The observations made at postmortem examination in cases of crush syndrome are distinctive and center in two sites: the kidneys and the skeletal musculature. Macroscopically the kidneys reveal only congestion and edema, but they exhibit well marked microscopic changes which center chiefly in the renal tubules. The glomeruli show no histologic alteration but do reveal the presence of an albuminous material in Bowman's capsule. The epithelium of the convoluted tubules and the loops of Henle contains some degenerative changes and may be shed and mingle within the tubules with eosinophilic coagulum. The striking observation is that of pigment casts, which may be present in the loops of Henle but more abundantly in the collecting tubules.

Observations concerning the urine are as follows: The volume is low. The specific gravity is fixed at about 1.015. The urine is acid. Albumin invariably is present. Leukocytes are commonly found. Erythrocytes have been found in several cases but are not always present. Granular pigmented casts are found in every case in which the condition is typical. In association with these facts, the reaction to the benzidine test for blood is almost always positive.

The shock exhibited in these cases is treated by the usual methods. The real problem concerns the treatment of the later-developing oliguria. Diuretic agents (such as hypertonic solution of dextrose, caffeine, mercury and others) have been used without effect. Large amounts of fluid have been administered in every case, and usually the only observed result has been an increase in the edema. Hot packs applied over the renal regions are of no apparent benefit.

Various surgical procedures have been suggested. These include amputation (performed in 1 case without success), incision through



the deep fascia in an attempt to reestablish circulation cut off by edema and decapsulation of the kidneys. The use of elastoplast on the edematous limb has been suggested.

Recently, several cases of recovery have been reported, and in these the success has been attributed to the administration of alkalis. The rationale of alkaline therapy is based on two facts: (1) that the patients all have marked acidosis and (2) that it is probable that, like hemoglobin, the pigment found in these cases is precipitated in the tubules if the urine is acid, whereas if the urine is alkaline the pigment will pass through without the infliction of renal injury.

Longland and Murray administered 360 grains (about 23 Gm.) of potassium citrate by mouth daily for four days and 480 cc. of a 3.3 per cent solution of sodium sulfate intravenously on the third of these days before the urine became alkaline. Henderson administered 540 cc. of a 3.3 per cent solution of sodium sulfate intravenously daily for four days. Blackburn and Kay administered 1,000 cc. of a 2 per cent solution of sodium bicarbonate rectally on the fifth day after injury and later (on the eighth day) started to administer sodium bicarbonate orally, giving a total of 96 Gm. in seven days.

At present it appears that the administration of alkali in doses sufficient to alkalinize the urine is of prime importance in the treatment of these patients. Presumably, the earlier the administration of alkali is started, the more likely is it to be of benefit.

*Anomaly.*—Anson, Pick and Cauldwell<sup>6</sup> discuss the anatomic aspects of renal anomalies. In serial dissection of 2 specimens of anomalous kidneys, they discovered anatomic features which are of surgical importance. These features are concerned chiefly with portions of the renal regions which could not or would not be studied in the course of the usual urologic operation or routine postmortem examination; these areas are the sites of complex arterial and venous anastomoses between renal vessels and almost all vascular channels of the abdominal wall.

The ectopic (pelvic) kidney lies in front of the sacral promontory, they state, just to the right side of the midline. Its renal artery and two renal veins follow an almost vertical rather than a transverse course. In passing along the kidney the vessels groove the renal parenchyma, and the sulci thus formed are more striking than the renal hilus.

Of almost equal importance is the set of vessels with which the ectopic kidney is brought into relation posteriorly and laterally. The

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6. Anson, B. J.; Pick, J. W., and Cauldwell, E. W.: *The Anatomy of Commoner Renal Anomalies: Ectopic and Horseshoe Kidneys*, *J. Urol.* **47**:112-132 (Feb.) 1942.

kidney rests on the common iliac artery and the corresponding veins; these in turn overlie the sacral plexus and the sympathetic trunk. The bed of the kidney is therefore composed almost totally of the large pelvic arteries and veins, an anatomic arrangement of grave importance in urologic surgery.

In the specimen of horseshoe kidney which they studied, the renal arteries and veins with the aorta and the inferior vena cava and the related adrenal and testicular blood supply formed a quadrilateral maze of vessels the boundaries of which were the mesenteric arteries above and below and the outer margins of the psoas major muscles on each side. Both sets of adrenal arteries were closely associated with superiorly placed renal arteries; as usual, they were numerous and complex, whereas the adrenal veins were solitary in arrangement. Sympathetic nerve plexuses crossed the isthmus of the fused kidneys to become the presacral nerve below the aortic bifurcation.

*Hydronephrosis.*—Hägenbach<sup>7</sup> reports 7 instances of hydronephrosis among children. In 6 cases the kidney was removed, and in the seventh case a large aberrant vessel was resected. In this case an examination of the patient nine years later showed hydronephrosis still present.

Sargent<sup>8</sup> discusses the basic principles governing conservative surgical operation in hydronephrosis. He states that hydronephrosis is not the unilateral disease that it has been so commonly thought to be. Nephrectomy for hydronephrosis in one kidney can and sometimes does initiate the rapid development of hydronephrosis on the opposite side.

Plastic reconstruction of the ureteropelvic juncture is a perfectly safe and practicable surgical procedure.

Once ureteropelvic obstruction has been successfully overcome (unless the kidney is hopelessly dead to begin with), there follows a succession of events—anatomic involution, decrease of infection and recovery of function that is always impressive and sometimes even unbelievable.

It is impossible by the use of any one particular method to correct the wide variety of pelvic deformities that are encountered, and Sargent believes that good results are most likely to be gained by fitting the proper procedure to the particular type of deformity at hand. Performance of protective nephrostomy is absolutely indispensable when the pelvis has been opened for a plastic surgical operation. A splinting

7. Hagenbach, E.: 7 Fälle von kindlichen Hydronephrosen, Schweiz. med. Wchnschr. 70:226-229 (March) 1940.

8. Sargent, J. C.: Basic Principles Governing Conservative Surgery in Hydronephrosis, J. Urol. 47:323-343 (March) 1942.

catheter is of considerable help, provided it is sufficiently small to fit loosely within the ureter. Wounds caused by plastic surgical operations on the ureter and the pelvis heal readily. Nephrectomy should be reserved for those cases of hydronephrosis in which the kidney is known to be utterly worthless and for those occasional cases in which plastic surgical procedures have been undertaken and have failed.

*Stone.*—Creevy<sup>9</sup> discusses nephrolithiasis caused by infection with members of the genus *Proteus*.

Organisms of this genus probably reach the urinary tract only through instrumentation, although Chute had 2 patients who had had no such history. The organisms are common residents of the human bowel, having been found on a single culture of the stools of 22 of 53 patients taken consecutively at random. The organisms may be present about the external urinary meatus and may be introduced by a urethral instrument, or may grow along the outer surface of an inlying catheter. Such a catheter, whether it is situated in the urethra, in a suprapubic fistula or in the kidney, may be contaminated either directly or from linen not grossly soiled. The route by which the organisms, once they have been introduced into the bladder, invade the kidneys is not definitely known. They may, however, arrive by way of the blood stream. Theoretically, of course, they may ascend the periureteral lymphatic vessels or the lumen of the previously diseased ureter or follow the lymphatic vessels from the ascending portion of the colon to the right kidney. The latter route may account for those infections which arise in the absence of instrumentation. According to the literature members of the genus *Proteus* are not common invaders of the urinary tract; they occurred in only 135 (5.4 per cent) of 2,502 cases of urinary infection in five reported series.

The relative infrequency of infection caused by these organisms is in striking contrast to the potential seriousness of the infection to the afflicted person. The peculiar menace of the organisms is their ability to break down the urea of the urine into carbon dioxide and ammonia, the latter of which makes the urine strongly alkaline.

The organisms are found in but a small proportion of instances of renal and ureteral lithiasis. Of 2,537 cases of stone collected from ten reports in the literature, data as to infection were complete in 2,191. In 65 per cent of these cases infection was associated with bacteria in the urine. In 6.2 per cent of the whole group and in 11 per cent of the cases of infection, members of the genus *Proteus* were found.

The organisms occur relatively more often in the presence of recurrent stones than in the presence of primary stones. Swift-Joly

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9. Creevy, C. D.: Nephrolithiasis Due to Infection with the *Bacillus Proteus*, *Surgery* 10:971-984 (Dec.) 1941.

and many others have found that nearly all recurrent stones are associated with infection and that if postoperative infection caused by urea-splitting organisms occurs recurrence is almost certain to take place. Chute reports that in 13 of 26 cases of recurrent stones the calculi were due to infection with organisms of the *Proteus* group, and Twinem found the organisms in 7 of 10 patients who had repeated recurrences after operation.

Once stones begin to form in the kidneys as a consequence of infection with these organisms, the outlook is black indeed unless stones, predisposing causes (particularly stasis and immobilization in recumbence) and the exciting organism all can be removed. If the urinary tract is normal except for the infection, the organisms can be easily killed by acidification of the urine and the administration of mandelic acid.

In summary, Creevy reports 13 cases in which nephrolithiasis secondary to infection by members of the genus *Proteus* occurred. In 11 of the 13 patients (84 per cent), the infection was known to have been introduced by catheters, such as are usually employed in nephrostomy or cystostomy. In 2, congenital anomalies of the urinary tract were present. In 9 (70 per cent), the calculi were bilateral; in 2, the calculi grew rapidly under observation. Five (38 per cent) of the patients died, 4 as a direct result of the infection and lithiasis and 1 from a surgical accident.

Treatment of the patients seen earlier in the series was entirely futile, but Creevy says that treatment is gradually improving for four reasons: (1) development of effective urinary antiseptic agents (sulfanilamide and especially sulfathiazole [2-(paraaminobenzenesulfon-amido)-thiazole]) and of the citrate-citric acid irrigants; (2) clear understanding of the mode of entrance of the organisms into the urinary tract; (3) appreciation of the extraordinary serious potentialities of these organisms, and (4) comprehension of the roles of predisposing factors, such as stasis and recumbency.

He concludes that the real solution of the problem lies, however, not in the removal of stones, relief of stasis and cure of infection but in the prevention of the entrance of the organisms into the urinary tract by adequate, painstaking and persistent attention to proper sterilization of catheters and their adjuncts, to their aseptic introduction and fixation and above all to the proper care of the systems draining urine from the body. To this end, he says, educational activities by informed urologists are imperative.

Priestley and Schulte<sup>10</sup> state that approximately 85 per cent of patients who have renal or ureteral calculi which require surgical

10. Priestley, J. T., and Schulte, T. L.: Simultaneous Bilateral Operation for Renal and Ureteral Calculi, *J. Urol.* **47**:255-257 (March) 1942.

treatment have stones in one side of the urinary tract only. In the remaining 15 per cent of cases bilateral calculi are present.

There are several types of cases in which the simultaneous bilateral operation might be of value. In the event of bilateral ureteral obstruction by stone it is of advantage to relieve the obstruction on each side at the earliest possible time. Especially is this important if a serious degree of infection is present. Should this condition exist on both sides at the same time, it seems worth while to relieve the obstruction to both ureters at the same operation, provided the patient presents himself as a fair operative risk. Likewise, if pyonephrosis with stone exists on one side and a simple stone readily removable by operation is present on the other side (particularly if it has caused or is causing obstruction), the bilateral simultaneous operation may be advisable. By this procedure renal function is maintained by removal of the stone on the side of the functioning kidney and the source of infection and possible postoperative complication presented by the pyonephrosis are removed at the same time.

There are other combinations of bilateral calculous disease in which use of the bilateral simultaneous operation may be optional. Such might be a virtually functionless kidney on one side associated with calculous disease and a single calculus in the opposite kidney. Likewise, bilateral single renal calculi, neither of which is causing urgent symptoms, with adequate renal function and little infection may or may not be removed at one operation; this depends on the discretion of the surgeon. In general there are two main types of cases in which the bilateral simultaneous operation may be considered, namely, the case in which the patient is in good condition with normal renal function and a readily removable calculus on each side and, in contrast, the case in which the patient is critically ill with serious calculous disease which is jeopardizing his well-being in each kidney or ureter, either of which by itself demands immediate surgical attention.

The obvious advantages of the simultaneous bilateral operation in addition to relief of an acute condition on both sides are largely economic. The period of hospitalization and disability is definitely reduced. Probably it is unwise to plan operation on both sides of the urinary tract for stone at one time if operation on either side is unusually difficult. Thus in the presence of large recurrent renal calculi the unilateral operation generally is enough for the patient at one time.

*Cyst.*—Lüdin and Howald<sup>11</sup> report a case of intrarenal cyst. The walls of the cyst were covered with calcium carbonate and phosphate crystals. The cyst was removed surgically, and healing took place

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11. Lüdin, M., and Howald, R.: Eine eigenartige, intrarenale Zyste, *Schweiz. med. Wchnschr.* 70:230-232 (March) 1940.

without incident. Lüdin and Howald discuss the possibility of the cyst's arising from an aberrant calix.

Rudström<sup>12</sup> reports a case in which a renal cyst containing about 2,000 small rounded concretions of approximately equal size passed spontaneously. There was no evidence of urinary infection. Analysis of the concretions showed them to be composed of an albumin stroma incrustated with calcium phosphates and carbonates. The cystic cavitation which filled with contrast medium from the renal pelvis on intravenous and retrograde pyelography was regarded as being an intrarenal solitary cyst that had invaded the renal pelvis. The renal cyst was thought to be the center of formation of the concretions. Rudström records another case of similar formation of a cyst (without concretions) and refers to 2 cases in the literature in which similar concretions in kidneys with cystic changes were reported.

*Tuberculosis.*—Braasch and Sutton<sup>13</sup> state that a difference of opinion exists as to the clinical data necessary to establishment of the diagnosis of renal tuberculosis in cases in which the diagnosis is doubtful. They believe that the presence of *Mycobacterium tuberculosis* in the renal urine obtained by catheterization as determined by positive results of inoculation of guinea pigs is not sufficient. They say that in addition there should be at least 3 to 10 pus cells per field under the high power objective and that in some cases positive urographic deformity will have to be noted to make the diagnosis certain. Among the 2,200 patients having renal tuberculosis observed at the Mayo Clinic, Rochester, Minn., during the years 1910 to 1934 inclusive, the condition of 291 (13 per cent) was diagnosed as bilateral renal tuberculosis. Eighty-seven of these 291 patients underwent nephrectomy, and 204 were not operated on. Braasch and Sutton say that nephrectomy in the treatment of bilateral renal tuberculosis is indicated only when there is a decided difference in the extent of the lesion in the two kidneys and only when the diseased kidney is the cause of the symptoms which require relief. They believe that a clearcut history of a period of dysuria and frequent micturition many years prior to examination with a history of recent recurrence is typical of bilateral involvement. Furthermore, it has been their impression that the previous occurrence of tuberculosis in other tissues often seems to increase the patient's resistance and may be conducive to a relatively good prognosis. They have noted also that in spite of advanced bilateral involvement of both kidneys the combined renal function is often normal or reduced only slightly. The incidence of hypertension among their patients was only a little higher than the average incidence of hypertension observed

12. Rudström, P.: Ein Fall von Nierenzyste mit eigenartiger Konkrementbildung, *Acta chir. Scandinav.* 85:501-510, 1941.

13. Braasch, W. F., and Sutton, E. B.: Prognosis in Bilateral Renal Tuberculosis, *J. Urol.* 46:567-578 (Oct.) 1941.

among adult persons traced. The clinical course of 167 patients revealed that the survival rate for patients traced for three years or more was about 72 per cent; for five years or more, 58 per cent; for ten years or more, 28 per cent, and for fifteen years, 16 per cent. Most of the patients who were living ten or fifteen years after examination were in a fairly normal condition except for a variable degree of frequency of micturition. It is the impression of the authors that previous concepts concerning expectancy of life in case of nonsurgical renal tuberculosis demand radical revision and that unless the indications for nephrectomy are definite in a case of bilateral disease it is well to give nature a chance rather than to intervene.

Wasserfallen,<sup>14</sup> in a review of the records of patients with tuberculosis in a sanatorium in Leysin, Switzerland, found that in 5.5 per cent of the patients with pulmonary tuberculosis and in 14.4 per cent of the patients with surgical tuberculosis renal tuberculosis was also present. Among none of the patients for whom the results of inoculation of guinea pigs had been positive was there found genuine tuberculous bacilluria. Wasserfallen does not think that nephrectomy is always immediately necessary, even when a positive diagnosis is reached.

*Tuberculoma.*—Bugbee<sup>15</sup> reports a case of tuberculoma of the kidney. The patient, a woman 30 years old, had pus and acid-fast bacteria in her urine. Excretory urograms disclosed normal filling of the right kidney and a filling defect suggestive of a tumor on the left. Nephrectomy was done on the left side, and the pelvis of the kidney was found to be filled with a smooth pink firm mass which had the appearance of a renal tumor. Zones of necrosis were not observed, nor were any tubercles seen. Sections made throughout the kidney, including the large nodule in the center, were involved by active tuberculosis and by the rapid formation of tubercles, with many endothelial cells and diffuse lymphoid infiltration. These tubercles were confluent and discrete and were found throughout the kidney from the pelvis to the cortex. The nodules on the surface also were seen to be tubercles.

Bugbee states that in this case an early stage of the disease was represented, in which the tuberculous process presented definite formation of tumor. Necrosis and cavity formation had not taken place, and although there were definite hemorrhagic portions in the bladder, the ureter apparently was not involved.

*Wilms's Tumor.*—Priestley and Schulte<sup>16</sup> review a series of 39 cases of Wilms's tumor in which nephrectomy had been performed five

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14. Wasserfallen, M.: *Remarques sur la tuberculose rénale*, Schweiz. med. Wchnschr. **70**:184-185 (March) 1940.

15. Bugbee, H. G.: *Tuberculoma of the Kidney: Report of a Case*, Tr. Am. A. Genito-Urin. Surgeons **34**:15-18, 1941.

16. Priestley, J. T., and Schulte, T. L.: *The Treatment of Wilms' Tumor*, J. Urol. **47**:7-10 (Jan.) 1942.

years or more prior to the follow-up study which they present. Six of the 39 patients, or 15 per cent, were living five years or more after nephrectomy. Various forms of treatment of Wilms's tumor, namely, irradiation alone, operation alone, irradiation followed by operation, operation followed by irradiation, and irradiation followed by operation and subsequently further irradiation, were considered. The authors favor the last form of treatment with a relatively short period of preoperative irradiation, usually accomplished within ten days to two weeks. In the exceptional case in which the tumor is small when it is first seen, immediate nephrectomy followed by postoperative irradiation can be employed. Twelve patients were treated by preoperative irradiation, nephrectomy and postoperative irradiation, and the results obtained in this group were the best of any. Three of these 12 patients (25 per cent) were living five or more years after operation at the time of the authors' report.

*Pyelonephritis.*—Gloor<sup>17</sup> reports 7 cases of shrunken or atrophic kidneys. In 5 of these the patients came to necropsy, and the pathologicoanatomic examination in all 5 cases confirmed the clinical diagnosis of renal hypoplasia.

Most of the patients were young; 6 of them were between 20 and 45 years of age. The blood pressure of these patients varied between 100 and 130 systolic and 80 and 100 diastolic; in 1 case in which glomerulonephritis complicated the situation there was terminal hypertension of 175 systolic and 120 diastolic. The value for urea varied from 51 to 339 mg. per hundred cubic centimeters of blood. Most patients have a fairly high degree of albuminuria. Results of microscopic examination were not typical; usually, a few pus cells and only rare casts appeared. A large number of leukocytes was found only in those cases in which secondary infection had occurred. The urine was sterile in 4 cases; in 3, numbers of *Escherichia coli* were observed.

The pyelograms all disclosed small, triangular renal pelves, the calices being close together (typical) and pyelograms depicting atrophic pyelonephritis.

Numerous associated anomalies, such as hypospadias, spina bifida and changes of the location of the ureteral orifices, suggested an anomalous origin of the renal condition. The smallest kidney weighed 15 Gm., and the largest, 90 Gm.

Histologic examination showed two different structures of tissue: (1) normally constructed renal parenchyma with well developed glomeruli and tubuli and (2) portions of stroma-like transformation of the entire parenchyma. Cysts of different sizes pressed closely together

17. Gloor, H. U.: Die hypogenetische Niere und ihre Bedeutung im Problem der renalen Blutdrucksteigerung, *Ztschr. f. urol. Chir. u. Gynäk.* 46:7-56, 1941.



and filled with a colloidal substance frequently were seen. Partial hyalinization of the glomeruli was pronounced.

Gloor notes that in all these cases hypertension was not found and states that hypertension as a rule results only when a large number of glomeruli are affected.

Likely, Lisa and Solomon<sup>18</sup> review 93 cases in which patients who had uremia came to necropsy. In this group were 32 patients with pyelonephritis. Twenty-two of these died of uremia. Most of the patients had degenerative cardiovascular renal disease. The series illustrates the importance of long-standing pyelonephritis as the basic pathologic condition in a large proportion of the mass of those patients seen in hospital practice who usually are grouped as having degenerative diseases.

*Hypertension and Renal Disease.*—Abeshouse<sup>19</sup> states that the diagnosis of essential hypertension should be made with great reservation. Every patient who has hypertension of unknown causation should be given the benefit of comprehensive study of the entire body, including complete urologic study. The value of this type of investigation is emphasized by the frequent occurrence of urologic lesions among hypertensive patients, as indicated in recent clinical and statistical reports.

Abeshouse says that the presence of a urologic lesion in a hypertensive patient must be carefully evaluated from the standpoint of causation, for not infrequently such a lesion is coincidental and bears little causal relation but may influence considerably the clinical course of the hypertension.

In some cases the blood pressure returns to and remains at a normal value after the performance of nephrectomy, an occurrence which can be attributed to the fact that unilateral renal disease was the primary factor responsible for the hypertension and that secondary arteriolar changes in the opposite kidney or in other parts of the body either were absent or had not progressed to an irreversible degree.

In other cases the end results from the standpoint of reduction in arterial blood pressure were not so striking after nephrectomy, i. e. the immediate effect was a transitory lowering of the blood pressure for a few weeks or months followed by a gradual return to preoperative values.

Abeshouse says it is important that an adequate period of time (at least a year) elapse after operation before the urologist attempts to evaluate the permanency and the extent of the reduction in arterial

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18. Likely, D. S.; Lisa, J. R., and Solomon, C.: Pyelonephritis, with Death in Uremia, *J. A. M. A.* **119**:397-400 (May 30) 1942.

19. Abeshouse, B. S.: Hypertension and Unilateral Renal Disease: Review of the Literature and Report of Sixteen Cases, *Surgery* **10**:147-200 (July) 1941.

blood pressure. In view of the uncertain end results that have been obtained and the insufficient period of observation mentioned in the reported cases, he thinks there is no justification for the consideration of nephrectomy as a panacea for the cure of hypertension in every case of chronic unilateral disease of the kidney.

Abeshouse concludes that every clinician and urologist should recognize the limitations of and contraindications to nephrectomy in the treatment of hypertension associated with unilateral renal disease. It must be remembered, he says, that nephrectomy may be fatal in instances of hypertension of long duration or in cases in which the clinical course is suggestive of so-called malignant hypertension.

Gibson<sup>20</sup> states that experimental evidence has shown that ischemia is the essential factor which causes hypertension in renal disease. Renal ischemia results in the liberation from the kidney of a vasoconstrictor or pressor substance called renin. Analysis of clinical reports indicates that many types of lesions of the kidney may cause hypertension. These lesions can be classed into three general groups: (1) gross vascular lesions of the renal artery or its branches; (2) the obstructive so-called uropathies, and (3) chronic inflammatory lesions. In all three groups, Gibson says, clinical evidence supports the experimental evidence which indicates that ischemia is the important factor in initiating hypertension.

Chronic infection appears to be the most important single causative factor in the production of renal ischemia. It is estimated that from 15 to 20 per cent of instances of malignant hypertension are caused by chronic pyelonephritis, even though in some cases the infection has run its course and has healed. Gibson thinks all patients who have hypertension should be given the benefit of complete urologic investigation as a part of their routine examination, even in the absence of signs or symptoms of disease of the urinary tract. Reasonable expectancy of improvement or cure of hypertension of renal origin can be hoped for by appropriate treatment of the pathologic process or processes thus revealed in the opinion of Gibson.

Powers and Murray<sup>21</sup> report a case of what is called juvenile hypertension, secondary to unilateral disease of the kidney. They classify the renal lesions as primarily neoplastic, obstructive, congenital or inflammatory. They state that thorough investigation of the urinary tract should be carried out for every child who has a previous history of pyelitis or pyelonephritis and who has symptoms referable to the

20. Gibson, T. E.: Hypertension and the Surgical Kidney, California & West. Med. 56:66-70 (Feb.) 1942.

21. Powers, J. H., and Murray, M. F.: Juvenile Hypertension Associated with Unilateral Lesions of the Upper Urinary Tract, J. A. M. A. 118:600-604 (Feb. 21) 1942.

central nervous system, the cardiovascular system, the gastrointestinal tract or the genitourinary tract. The same investigation should be pursued in every case of unexplained juvenile hypertension. If disease of one kidney is discovered, the patient should be treated by operation, provided the function of the opposite kidney is essentially normal and the general condition of the child is adequate for him or her to withstand surgical intervention.

The authors say that with the exception of cases in which hypertension was secondary to renal neoplasm the immediate results of operative treatment in all reported cases, including the one they contribute, have been excellent. Too little time has yet elapsed for it to be possible to state with certainty that the hypertension in any case has been permanently relieved, they say.

Allen<sup>22</sup> discusses peripheral ligation in relation to blood pressure and states that the dog is highly subject to psychic or nervous hypertension, apparently to a greater degree than is man. The results of ligation of various parts of the body, duplicating those previously obtained concerning the kidneys, confirm the interpretation that the phenomenon is not humoral or specific to the kidneys but is purely nervous.

A strong psychic factor is obvious in all the experiments in which ligation or clamping of the kidneys, the testes, the legs, the tail and the ears was done, but the occurrence or persistence of some elevation of pressure under conditions of mild anesthesia or psychic quietness, so to speak, indicates that an additional nervous mechanism, apparently reflex, operates.

Without prejudice to the results of other writers who have demonstrated the production of a hypertensive substance in the asphyxiated kidney under special conditions, results of the present experiments, Allen says, show that the secondary increase in pressure which follows prolonged ligation of explanted kidneys sometimes may be matched by similar occurrences with the testes and tail, in which case it is evidently a nervous response to the painful local inflammation. Since acute hypertension arising from ligation of organs or from simple excitement occurs in epinephrectomized animals, Allen suggests that the adrenal bodies apparently are not concerned in the process.

Braasch, Walters and Hammer<sup>23</sup> report that hypertension frequently was found in association with a unilateral lesion of the kidney and that rather often it could be relieved by surgical operation. They have analyzed records of a group of 1,184 patients who underwent renal

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22. Allen, F. M.: *Peripheral Ligations in Relation to Blood Pressure*, *J. Urol.* **47**:431-439 (April) 1942.

23. Braasch, W. F.; Walters, W., and Hammer, H. J.: *Hypertension and the Surgical Kidney*, *J. A. M. A.* **115**:1837-1841 (Nov. 30) 1940.

surgical exploration and found that the incidence of hypertension in this group was no higher than that found in a group of patients whose records were taken at random. They found also that the renal disease amenable to surgical treatment which occurs most often in association with hypertension is atrophic pyelonephritis. Seven of 10 patients (70 per cent) who had this condition were relieved of their hypertension. Hypertension was observed in 161 patients, or 20.3 per cent, of 793 for whom operation was performed for renal stone. The authors say that the role of secondary infection is important, since hypertension occurred in 22.5 per cent of cases in which infection was manifest and in only 5.7 per cent of cases in which there was no infection. The blood pressure returned to normal and remained normal after surgical intervention in approximately 23 per cent of the cases in which hypertension had been present preoperatively. Braasch, Walters and Hammer note that hypertension was present in approximately 14 per cent of patients with hydronephrosis without stone on whom operation was performed. Among the 29 patients who had had hypertension preoperatively there were 10, or 34.4 per cent, whose blood pressure returned to normal and remained so for one year to five years. Hypertension was observed in only 12, or 7.6 per cent, of the 158 patients with renal tuberculosis whose records were studied. Eleven of these patients were traced, and among these the blood pressure of 7 returned to normal. Hypertension was found in 38 cases, or 29.7 per cent, of 137 cases in which operation had been performed for renal adenocarcinoma. According to the authors there are not enough cases of renal neoplasm other than hypernephroma to allow an accurate survey of each type to be made. Hypertension was noted in 6 cases of epithelioma of the renal pelvis, and the blood pressure returned to normal in only 1 case. The blood pressure was recorded in 18 cases of Wilms's tumor and definite hypertension was noted in only 5. Among the 21 patients with hypernephroma complicated by hypertension, the blood pressure of 9 returned to normal; 3 of the patients experienced a temporary decrease in blood pressure and subsequently a return of hypertension. Of particular interest was a case of polycystic disease with hypertension in which one kidney had become functionless as a result of diffuse infection. The blood pressure of the patient decreased to normal after nephrectomy and remained normal for the year that the patient was followed.

Of further interest to the authors was a series of 14 patients whose blood pressure had been normal prior to conservative renal operation and in whom hypertension developed after operation. Urologic examination of these patients revealed evidence of reduced function and persistent infection in the kidney which previously had been subjected to operation. After removal of the kidney, the blood pressure of the

patients returned to normal. The authors conclude that a postoperative increase in blood pressure apparently occurs more frequently after a conservative operation for renal and ureteral lithiasis than it does after operations for other lesions. Renal insufficiency was not found to be causative of hypertension in the cases in which renal surgical operation had been performed. Since hypertension is caused by factors other than those relative to the kidney in most cases, the authors conclude that nephrectomy may be contraindicated in cases in which hypertension accompanies a surgical renal lesion, if any of the following factors are present: (1) bilateral renal disease so extensive that removal of one kidney would be of no benefit; (2) existence of hypertension of long standing with such extensive secondary degenerative lesions in other organs that removal of a diseased kidney would no longer influence the subsequent clinical course; (3) evidence of advanced renal insufficiency, and (4) existence in another organ of an unrelated serious lesion which in itself might be regarded as inoperable.

Wilson and Chamberlain<sup>24</sup> discuss unilateral renal ischemia associated with hypertension and report a case in which a 12 year old girl had severe headache, partial blindness and blood pressure of 230 systolic and 170 diastolic. Cystoscopy indicated that she had a small, functionless right kidney. This kidney was removed through a surgical incision and was found to weigh only 11.5 Gm. It was scarred, atrophic and fibrotic. After removal of this kidney the blood pressure decreased, and during the next year it remained at 120.

To ascertain whether there was any association between perinephritis and hypertension, Braasch and Wood<sup>25</sup> reviewed a series comprised of 70 patients encountered consecutively during a ten year period in whom the primary disease process was perinephritis. This study was instigated by the work of Page in 1939, who reported the development of hypertension in dogs after the application of a loose jacket of cellophane to either one kidney or both kidneys. In the entire series of 70 cases there were only 3 in which some correlation of hypertension with perinephritis might be established, and the authors conclude that the clinical association between perinephritis and hypertension is so slight as to be of little or no significance.

#### URETER

*Obstruction.*—Hoffman<sup>26</sup> has studied a series of 97 patients in whom ureteral obstruction followed radiation treatment of cancer of the cervix,

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24. Wilson, C. L., and Chamberlain, C. T.: Unilateral Renal Ischemia Associated with Hypertension: Case Report, *J. Urol.* **47**:421-430 (April) 1942.

25. Braasch, W. F., and Wood, W. W., Jr.: Clinical Perinephritis and Blood Pressure, *Proc. Staff Meet., Mayo Clin.* **17**:52-54 (Jan. 28) 1942.

26. Hoffman, P. E.: Ureteral Obstruction Following Irradiation Treatment of Cancer of the Cervix, *West. J. Surg.* **50**:69-72 (Feb.) 1942.

dividing them into different groups depending on the severity of the disease.

In group 1, all members of which were treated with radium only, there was only 1 instance of ureteral involvement during the three year period in which these patients were studied. Renal pain developed in the patient after two years, and she was found to have stricture. She rapidly improved and became symptom free after a series of ureteral dilations.

In group 2, comprised of 23 patients, 18 received radium and 5 received radium plus high voltage roentgen therapy. Only 1 patient in this group was found to have any initial renal pathologic process. She had slight hydronephrosis on the right, which after a series of ureteral dilations did not progress. Three of these patients had died at the time of Hoffman's report, but they had no involvement of the urinary tract. In 1 patient after a year there developed an obstruction of the right ureter 3 cm. from the ureteral orifice, with complete loss of function of the kidney, in spite of repeated dilations.

In group 3, composed of 40 patients, the treatment of 37 was high voltage roentgen therapy plus radium, and of 3, radium alone. The initial urograms disclosed that 16 had some type of renal pathologic process. Among 4 of the 24 patients who did not have any renal pathologic process on admission, unilateral obstructive ureteral lesions developed within six months, and 2 others had died at the time of Hoffman's report—one of metastasis to the lungs and the other of metastasis to bone. The other 18 had remained free of ureteral obstruction to the time of Hoffman's report.

Of the 20 patients with renal involvement, 6 died within three years. Of the 21 patients in group 4, 9 received high voltage roentgen therapy only; 2, radium therapy, and 10, high voltage roentgen therapy plus treatment with radium. The initial urograms disclosed that 13 had a ureterorenal pathologic process of some type. All the 8 patients who had no urologic involvement were living after three years (at the time of the Hoffman report). Three patients who had urinary involvement when first seen experienced progressive total loss of function in the affected kidney with compensatory hypertrophy taking place in the other kidney. Ten patients died within or shortly after three years. In every instance necropsy revealed marked involvement of the ureters with the inevitable effect on the kidneys.

Hoffman's procedure has been, he says, to dilate the ureters, and generally he has used the direct vision air cystoscope and Kelly catheters of sizes up to F 15 at intervals of ten to fourteen days. Twenty-four patients have been treated in this manner, but in most instances there has been a gradual diminution in the ureteral lumen until it became impossible to pass a dilator past the site of obstruction. Eleven patients

were more intensively treated in the hospital for periods of two to three months. Catheters were passed to the renal pelvis and left in place for periods of twenty-four hours. This procedure generally was repeated within two to four days. There was gradual shrinking of the ureter in spite of this treatment, and finally even small catheters could not be passed, and inevitable loss of the kidney resulted. In only 1 case was a permanent good result produced by ureteral dilation. Hoffman concludes that intensive ureteral dilation of the affected ureter as a means of alleviation of this condition has proved disappointing and says that other methods must be considered.

Wharton<sup>27</sup> presents reports of 7 cases of bilateral simultaneous ureteral obstruction. All the patients had uremia to a greater or a less degree. All would have died if the urinary obstruction had not been relieved. Necropsy of 1 patient who did die disclosed carcinoma of the bladder which surrounded and constricted both ureters. Consideration of these cases makes certain facts clear, Wharton says. Although these facts are undoubtedly well known, these cases show that the layman does not appreciate their significance and that many physicians fail to realize the potential danger of urinary stasis and infection. Among these basic facts are the following:

Chronic pyelonephritis may eventually destroy the kidneys. If it is accompanied by stasis, the damage is increased. The terminal pathologic lesion may be hydronephrotic or pyonephrotic atrophy of a contracted kidney. Hydronephrosis and hydroureter are the usual results of urinary obstruction and infection. But this is not always the case. The pelvis of the kidney may be contracted and smaller than normal, even in the presence of a dense and almost impassible ureteral stricture. Stricture may be complete or incomplete. Both types are of equal potential damage to the kidney. They differ chiefly in the rate at which the damage is inflicted.

An impassable or complete ureteral stricture is easily recognized according to Wharton. The difficulty arises in detection of the incomplete type, especially if the urologist uses a fine catheter. In the interpretation of findings a history of urinary infection and the general clinical picture are just as important as and maybe more enlightening than the urologic observations made at the moment. Correct management of the patients is a matter that requires sound judgment.

Urinary infection and obstruction frequently are insidious. Wharton says that they may be completely asymptomatic, progressing silently until irreparable damage has been inflicted. Elimination of these conditions, even if they are apparently asymptomatic, is essential if renal health is to be conserved.

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27. Wharton, L. R.: Simultaneous Obstruction of Both Ureters, with Uremia: Report of Seven Cases, *J. Urol.* **47**:133-140 (Feb.) 1942.

*Tumor.*—Cook and Counseller<sup>28</sup> report 18 cases of primary epithelioma of the ureter, the diagnosis being proved in each case by operation. The tumors were graded as follows: 1 was of grade 1; 9 were of grade 2; 7 were of grade 3, and 1 was of grade 4. Of the 10 patients who had grade 1 or grade 2 tumors, 7 were living (1 nine years; 2, three years; 1 two years, and 3, less than one year) at the time of the report. Of the 8 patients who had tumors of grade 3 or 4, only 1 was living; he had been alive for eight years after operation at the time of the report. Hematuria and pain are the two important symptoms. Although excretory urograms frequently may suggest the diagnosis, retrograde pyeloureterography is necessary in most instances to reveal the actual deformity and to establish the diagnosis. Cook and Counseller believe that the treatment is surgical and that complete extirpation of the kidney, the ureter and the ureterovesical segment of the bladder should be done. All periureteral adipose tissue should be removed with the ureter because of the tendency of this particular type of neoplasm to extend through the wall of the ureter.

*Ureterocele.*—Thompson and Greene<sup>29</sup> report results of clinical study of 37 cases of ureterocele and emphasize the cause, the diagnosis and the treatment of this condition. The causation of ureterocele is a somewhat controversial question, for the condition is considered by some to be congenital in origin and by others to be of an acquired nature. The consensus favors a congenital origin; however, in certain cases ureterocele has been observed to have been acquired. Twenty-five of the 37 patients were female, and 12 were male. The youngest patient was 9 years of age; the oldest, 64 years. Approximately two thirds of the 37 patients were between 30 and 50 years of age when the ureterocele was first detected. There is nothing characteristic about the symptoms of ureterocele. Pain was the most frequent symptom noted, but vesical symptoms, such as urinary frequency, dysuria and nocturia, often occur. Less frequently, hematuria (gross blood) and the passage of urinary calculi may occur. Five patients without symptoms referable to the urinary tract were studied urologically in an attempt to find the cause of obscure abdominal symptoms; in each case ureterocele was discovered.

Thompson and Greene describe the cystoscopic appearance of ureterocele and emphasize the variations in appearance which depend on the size of the lesion. As observed in an excretory cystogram, a ureterocele appears as a spherical or sausage-shaped filling defect or as an accentuation of the medium situated near the trigonal region and in line with the

28. Cook, E. N., and Counseller, V. S.: Primary Epithelioma of the Ureter, J. A. M. A. **116**:122-126 (Jan. 11) 1941.

29. Thompson, G. J., and Greene, L. F.: Ureterocele: A Clinical Study and a Report of Thirty-Seven Cases, Proc. Staff Meet., Mayo Clin. **17**:133-136 (March 4) 1942.



terminal portion of the ureter. A fine distinct halo occasionally is noted immediately about the ureterocele. In only 4 of 21 cases in which studies by excretory urography were made was the diagnosis of ureterocele established without the necessity of cystoscopy. In 1 other case the excretory urogram merely was suggestive of ureterocele.

Thompson and Greene state that if no symptoms of ureterocele are present and if the rest of the urinary tract shows no abnormality no immediate treatment is necessary; however, the patient should be informed of the presence of ureterocele in case symptoms develop in the future. In 9 of the 37 cases received no surgical or urologic measure was necessary. Cystoscopic dilation of the mouth of the ureterocele by means of ureteral bougies and catheters was employed in only 3 cases. Transurethral fulguration of the ureteral orifice or, better than that, ureteromeatotomy can be expected to yield the most satisfactory results. If the ureteral orifice cannot be located definitely, the most accessible point in the ureterocele may be selected for fulguration or incision. The incision should be large—equal to the diameter of the dilated ureter. Occasionally, the incision may need to be 2 or 3 cm. in length. Stones, if present, can be removed from the ureterocele at the time ureteromeatotomy is performed. In case serious renal damage has occurred, the performance of some surgical procedure on the kidney may be necessary. The authors say that the results of transurethral meatotomy have been satisfactory. In no case has it been necessary to perform nephrectomy at a later date, nor has it been necessary in any case to open the bladder suprapubically for additional treatment of the ureterocele. There was no death in the series of 37 cases.

*(To Be Concluded)*

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